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THE DEVELOPMENT OF TUBERCULOSIS IN THE APPARENTLY HEALTHY ADULT[1]

ARTHUR B. ROBINS[2]

Mortality has always been the measure most commonly used in the study of the epidemiology of tuberculosis. The reasons for this are obvious. Mortality is easily determined within the limits of completeness and accuracy of death registration. Death registration is compulsory by law and the required personal statistical particulars make it possible to enumerate deaths by age, sex, race and occupational groups. The deaths in these groups can in turn be related to the populations in which they occur and specific mortality rates established.

The use of mortality statistics, however, has not been confined to the purpose for which they are a relatively accurate measure. Such statistics have been made the basis of assumptions concerning other factors in tuberculosis. One such factor is prevalence which has been related to mortality in the "Framingham standard" which postulates that there exist 9 active and 9 arrested cases of tuberculosis for each annual death from the disease. The Framingham standard is based on a demonstration conducted from 1920 to 1923 in the small semi-industrial community of Framingham, Massachusetts. In this demonstration an attempt was made to determine the number of cases of tuberculosis in the community during the period of the study. X-ray was used in the examination of a large proportion of the population but not in all. Coöperation, though good, was not complete. The findings obtained were compared with the number of known tuberculosis deaths during the period and the Framingham standard derived (1). This formula, which possessed a very definite usefulness at the time and place it was established, has certain obvious limitations. It was obtained more than nineteen years ago in a small semi-urban community composed almost entirely of white persons. It can only be applied to the population as a whole and does not permit the estimation of morbidity in different age, sex and race groups. Its validity in estimating the prevalence of tuberculosis in communities of a different character than Framingham, and at later dates, is open to serious question.

Mortality statistics have also been used in estimating the incidence of tuberculosis. This is best illustrated by the standards of the *Appraisal Form for Local Health Work* of the American Public Health Association. In the current edition (1938) the following statement is made: "Formal case reporting is an almost universal requirement and the ratio of newly reported cases to annual deaths over a period of years is an accepted index of progress that is made in case discovery. In areas where little concern has previously been given to tuberculosis an increase of attention will readily develop a reporting ratio of between two and three new cases per death. As the program develops this may

[1] Presented before the Medical Section at the 38th annual meeting of the National Tuberculosis Association, Philadelphia, Pennsylvania, May 8, 1942.

[2] Bureau of Tuberculosis, Department of Health, New York City.

fall slightly below two, but as earlier cases are discovered and deaths from this cause are postponed or prevented, the ratio will return to approximately two cases per death" (2). Since the number of newly reported cases, and particularly early cases, is an expression of the rate of development of tuberculosis in the population, complete dependence of incidence on mortality is predicated in the Appraisal Form standard.

The relationship of prevalence and incidence to deaths from tuberculosis becomes of particular importance when applied to groups with markedly different mortality rates. In the large cities of the East the most important of these groups is the Negro population. The death rate among the colored in New York City in 1938 was 255 per 100,000 population, among whites 41, the rate being more than six times as high in the colored. Reasoning on the basis of the standards above, the assumption has frequently been made that the prevalence and incidence of tuberculosis are correspondingly higher in the Negro group.

Prevalence of tuberculosis in a given population can be exactly ascertained only by X-raying all of its members. This is extremely difficult even in small communities and is impossible in large cities. As a result sampling studies must be employed. In such studies certain segments of the population are examined and the tuberculosis morbidity determined. The amount of tuberculosis in the entire group is then estimated from the findings in the sample. If the sample is representative and is sufficiently large, valid conclusions concerning the whole population can be drawn. Similarly the incidence of tuberculosis in the group can be discovered by reëxamining the healthy members at stated intervals and ascertaining the number of new cases of tuberculosis which have developed. The sampling technique is applied as in determining prevalence, and the incidence rate for the entire population estimated. The same qualifications in regard to character and size of sample hold.

In recent years many such sampling surveys, based on tuberculin test selection and X-raying of the reactors or universal X-ray examination, have been conducted. For the most part they have been highly selective and confined to students, medical and nursing personnel, inmates of mental hospitals and prisons and certain groups of industrial employees. Prior to 1934, however, no systematic attempt to determine the prevalence of tuberculosis in a large city in this country had been made. Since that time surveys of various portions of the population of New York City have been conducted and close to 400,000 people have been X-rayed (3). As most of the groups contained some Negroes, and one group was composed predominantly of members of the Negro race, it was possible to study the racial prevalence of tuberculosis.

The findings were completely in discordance with the results anticipated from the application of standards based on mortality statistics. In Negro individuals fifteen to twenty years old, with mortality rates ten to fifteen times those of white persons of the same age, the morbidity was only 2 to 3 times as great. In individuals over twenty years of age, among whom the Negro death rates are three to ten times as high as the rates for the white, less tuberculosis was found

among the Negroes. Other surveys of apparently healthy individuals have consistently confirmed these findings. Among enlisted men in the United States Army (Roth (4)), industrial employees (Cummings, Downs and Berg (5)), prisoners and homeless men, fewer cases of tuberculosis were discovered in Negroes over twenty-five. This disparity was not accounted for by environmental differences in the two races, and was present in respect to both active and arrested tuberculosis.

TABLE 1

Distribution of 8,731 persons X-rayed in follow-up study by age, sex and race—Harlem, 1938

AGE GROUP	NUMBER X-RAYED	SEX		RACE			SEX AND RACE					
							White		Negro		Puerto Rican	
		Male	Female	White	Negro	Puerto Rican	Male	Female	Male	Female	Male	Female
years												
5– 9.9	12	4	8	1	11		1		3	8		
10–14.9	110	49	61	7	101	2	1	6	46	55	2	
15–19.9	589	262	327	31	533	24	8	23	244	289	9	15
20–24.9	563	199	364	32	483	48	9	23	173	310	17	31
25–29.9	1,047	328	719	40	921	85	9	31	284	637	34	51
30–34.9	1,256	434	822	94	1,081	81	39	55	357	724	38	43
35–39.9	1,319	473	846	102	1,148	69	51	51	387	761	35	34
40–44.9	1,141	424	717	109	970	61	57	52	338	632	28	33
45–49.9	852	307	545	103	721	28	54	49	243	478	10	18
50–54.9	679	266	413	72	581	26	37	35	218	363	11	15
55–59.9	540	226	314	48	476	16	29	19	193	283	4	12
60–64.9	337	143	194	51	276	10	34	17	106	170	3	7
65–69.9	194	83	111	32	158	4	17	15	64	94	2	2
70–74.9	72	34	38	14	57	1	13	1	21	36		1
75–79.9	16	8	8	9	7		5	4	3	4		
80–84.9	4	2	2		4				2	2		
Total.....	8,731*	3,242*	5,489*	745	7,528	455	364	381	2,682	4,846	193	262
Average age.	39.0	39.5	38.7	43.6	38.7	35.7	46.7	40.6	38.8	38.7	35.0	35.9

* Includes persons of other races.

In an attempt to throw further light on the problem it was decided to study the incidence of tuberculosis in the white and Negro population. The survey of home relief recipients in Harlem had revealed approximately 40,000 individuals whose X-ray films in 1937 showed no evidence of pulmonary tuberculosis. An attempt was made to have these persons return in 1938 for an additional X-ray examination. After considerable effort 8,731 persons, a little better than 20 per cent of the original group, were re-X-rayed. The age, sex and race distribution of these 8,731 individuals is shown in table 1. The average age of the white group was highest and of the Puerto Rican lowest, the differences in the average ages of the three groups being significant.

Twenty-five cases of tuberculosis were found among the 8,731 individuals

re-X-rayed. Twenty-four had chronic pulmonary tuberculosis and one had idiopathic pleurisy with effusion. The age, sex and race distribution of the 25 cases is given in table 2. The age of the individuals at the time tuberculosis was first discovered is of special interest. The average for all cases was 33.3 years and for the Negroes who developed lesions 33.4 years. The mean for Negro males was 38.9 years and for Negro females 29.2 years, a difference of statistical significance. More than two-thirds of all cases occurred in individuals over thirty years of age, irrespective of race.[3]

The essential clinical findings in these 24 pulmonary cases are shown in table 3. The average interval from negative X-ray films to the subsequent ap-

TABLE 2

Age, sex and race distribution of 25 cases of tuberculosis discovered in follow-up study—Harlem, 1938

AGE GROUP	TOTAL CASES	SEX		RACE								
				White			Negro			Puerto Rican		
		Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female
(*years*)												
15–19.9	3		3				3		3			
20–24.9	4		4				2		2	2		2
25–29.9	1	1					1	1				
30–34.9	7	4	3				7	4	3			
35–39.9	4	1	3				4	1	3			
40–44.9	3	2	1				2	1	1	1	1	
45–49.9	1	1		1	1							
50–54.9	1	1					1	1				
55–59.9	1	1					1	1				
Total.....	25	11	14	1	1		21	9	12	3	1	2
Average age in years*	33.3±2.2	38.9	27.4				33.4±2.3	38.9±3.3	29.2±2.7			

* Calculated from ungrouped data.

pearance of the tuberculous lesion was 13.8 months for the entire group, and the differences by race and sex were not of significance.

Eighteen of the 24 pulmonary lesions were considered exudative or caseous-pneumonic and the remaining 6 productive in type. The white male had a productive lesion. Two of the exudative lesions occurred in Puerto Rican females, one in a Puerto Rican male and the remaining 15 in Negroes.

[3] Mean age of cases at time of development of tuberculosis:

	years
All cases.....	33.3 ±2.2
All Negroes.....	33.4 ±2.3
All Negro males.....	38.9 ±3.3
All Negro females.....	29.2 ±2.7

In 18 patients the lesion was in the right lung, in 5 in the left lung, and in one in both lungs at the time of discovery. This tendency for tuberculosis to develop in the right lung was not influenced by the age of the patient or the pathological nature of the process but was markedly affected by sex. Eleven of the 13 cases in females were right-sided, whereas 7 males had lesions on the right, 3 on the left and one on both sides. The difference in the number of cases occurring on the two sides is statistically significant in females but not in males. Its biological importance, of course, remains to be established.

Because of the character of the survey a history could be obtained in only 16 cases. It was negative for known contact in 11. In only 2 of the remaining 5 cases was the contact history definite and of consequence.

TABLE 3

Clinical findings in 24 cases of pulmonary tuberculosis discovered in follow-up study—Harlem, 1938

GROUP	INTERVAL BETWEEN NEGATIVE AND POSITIVE X-RAYS	TYPE OF LESION		SIDE OF LESION			HISTORY OF CONTACT			DURATION OF SYMPTOMS			PRESENT STATUS OF CASE					INTERVAL FROM DIAGNOSI TO DEATH
		Exudative or caseous pneumonic	Productive	Right	Left	Bilateral	Positive	Negative	History not obtained	None	Less than three months	More than three months	Active	Arrested	Left city	Not found	Dead	
	Months																	*Months*
All cases.....	13.8	18	6	18	5	1	5	11	9	7	6	3	4	6	3	3	7	8.0
All males.....	15.1	9	2	7	3	1	3	4	4	2	4	1	3	3	1	1	2	5.0
All females....	12.6	9	4	11	2	0	2	7	5	5	2	2	1	3	2	2	5	9.2
All Negro	13.6	15	5	15	4	1	5	8	8	6	4	3	4	4	2	3	7	8.0
Negro male...	15.3	8	1	6	2	1	3	2	4	1	3	1	3	2	1	1	2	5.0
Negro female.	12.3	7	4	9	2	0	2	6	4	5	1	2	1	2	1	2	5	9.2
All white.....	14.0	0	1	1	0	0	0	1	0	1	0	0	0	1	0	0	0	
All Puerto Rican.....	14.0	3	0	2	1	0	0	2	1	0	2	0	0	1	1	0	0	

Only 9 patients gave a history of symptoms prior to the discovery of their lesions by X-ray. In 6 the symptoms were of less than three months, and in the other 3 of longer duration. Seven patients denied symptoms were present and in 9 no history was obtained.

The present status of 18 of the cases is known. Three have not been found and 3 are reported to have left the City permanently. The latter 3 cases were active at the time they moved. Seven individuals have died, all of whom were Negroes. Two were males, thirty-one and fifty-seven years old, who had caseous lesions at the time of onset. Five were females, sixteen, seventeen, thirty-one, thirty-five and thirty-eight years of age, respectively. The sixteen year old girl had a productive lesion and the others exudative or caseous-pneumonic tuberculosis. The interval from first diagnosis to death was eight months, the average in males

being five months and in females 9.2 months. The longest duration of life after the establishment of the diagnosis was fifteen months and the shortest three months. The interval from negative X-ray film to death was 20.1 months. Since January, 1940, no deaths from tuberculosis have occurred in the group.

Four cases are still classified as active, 3 Negro males and a Negro female. The 6 arrested cases include 2 Negro males, 2 Negro females, a white male and a Puerto Rican female. The ages of these cases vary from sixteen to forty years and 3 of the 6 have productive lesions. Half received adequate institutional care and 2 of the other 3 had small productive foci. One Puerto Rican male developed a small exudative lesion which cleared considerably in a short period and he was subsequently classified as negative and discharged.

The incidence of tuberculosis in the entire group was 2.9 per thousand. In the white population it was 1.3 per thousand, in the Negro population 2.8 per thousand, and in the Puerto Rican population 6.6 per thousand. The differences in rates in the three races are not statistically significant. Since the mean period of observation was 14.2 months, the annual incidence rate in the group as a whole was 2.4 cases per 1,000 population.

Certain factors affecting the reliability of the sample used in this study were investigated further. One was the degree to which the 8,731 individuals who returned for X-ray examination were representative of the entire group examined. During the three-year period of the Harlem survey 65,459 persons had been X-rayed and data as to their age, sex and race were available. Statistical analysis indicates that the group of 8,731 persons re-X-rayed was older and contained a significantly higher proportion of Negro females than the entire group, but that in other respects the two populations were homogeneous.

Another possible factor was the extent to which the 8,731 persons who returned for X-ray examination might have been selected by the removal through illness or death of persons who had already developed tuberculosis. To test this possibility a sample of approximately 4,000 persons who failed to return for X-ray examination was chosen at random from the persons whose X-ray examination in 1937 was negative. This group was characteristic of the entire population X-rayed in regard to age and sex but contained a higher proportion of white persons. The names of these 4,033 individuals were checked against the central roster of reported cases of tuberculosis and the register of tuberculosis deaths to determine the number of cases of tuberculosis that had developed since their original negative X-ray film in 1937. Nine such cases were found, an incidence of 2.2 per thousand. Seven were Negroes, one white and one Puerto Rican. The incidence rate in the Negro group was 3.2 per thousand.[4] The average interval from negative X-ray film to date of report was 18.7 months. The ages of the 9 cases at the time of negative X-ray films were sixteen, eighteen, nineteen,

[4] Incidence of tuberculosis by race—cases per 1,000 persons:

All cases	2.2
Negro	3.2
White	1.1
Puerto Rican	1.0

nineteen, twenty-six, twenty-nine, thirty-four, forty-eight, fifty-six years. At the time of writing, 7 of these 9 patients had died and the other 2 were still classified as active.

As it was not possible to rule out the presence of asymptomatic tuberculous lesions among members of this group, an annual incidence rate comparable to that obtained in the group who returned for X-ray examination could not be computed. However, the findings do not indicate that the rates were appreciably different in the two groups, and the evidence does not suggest that the incidence rate of 2.4 per thousand per year has been lowered by the removal of an undue proportion of persons who have already developed tuberculosis. From the above data we believe that the annual incidence rate of 2.4 per thousand can be accepted as representative of the home relief population of Harlem.

Comparison of our findings with those of other studies would indicate that an annual incidence rate of 2.4 per thousand among home relief recipients in Harlem, 86.2 per cent of whom were Negro, is not very much higher than the rates observed in other groups. Fellows (6) has reported incidence rates varying from 2.23 per thousand per year to 2.69 per thousand per year among home office employees of the Metropolitan Life Insurance Company, a group composed predominantly of young white females. Cummings, Downs and Berg in a study of 5,000 steel mill workers, 83.5 per cent of whom were white, found an apparent incidence of 2.3 per thousand per year. Among enlisted men in the United States Army, including only 4 to 5 per cent Negroes, the annual morbidity rate from tuberculosis was 2.10 per thousand in the white troops and 2.56 per thousand in the Negro troops (Roth). Since the mortality rate in Negroes over twenty years of age is three to ten times that of white persons of the same age, no correlation between incidence and mortality can be demonstrated on the basis of the above studies.

What, then, is the relationship of incidence, prevalence and mortality in tuberculosis? The basic factor in the epidemiological pattern is the incidence, or number of new cases developing annually. At the same time that new cases are being added, other cases are being removed by death, which is expressed by the mortality rate. The resultant of these two factors is the prevalence, or amount of tuberculosis present at any given moment. Incidence is determined by the number of cases in the community which serve as foci of infection, the opportunities for contact and the complex of intangibles known as general and specific susceptibility. Mortality is influenced by resistance, general, racial and individual, and the effects of therapy, and is best expressed by the case fatality rate, or proportion of cases dying in a given period of time. When the elements necessary to produce an incidence of a certain level are present in one group, and the case fatality rate is high in this group, a definite prevalence will result. If, in another group with about the same incidence rate, the case fatality rate is considerably lower, a higher prevalence will be observed. Two such sets of circumstances provide an adequate explanation for the differences in incidence, prevalence and mortality noted in the Negro population in our study and in the white populations in the studies cited above. Attempts to reconcile these

observations with rigid standards calling for a fixed ratio of prevalence or incidence to mortality only lead to confusing and contradictory results. A clear picture of the epidemiology of tuberculosis must come from accurate determination of incidence and case fatality rates and their precise application to specific situations and not from the use of artificial formulae.

SUMMARY

The incidence of tuberculosis in the apparently healthy adult population of the Harlem area of New York City was determined by re-X-raying a group of home-relief recipients whose previous films had shown no evidence of pulmonary tuberculosis. The group consisted of 8,731 persons, 86.2 per cent of whom were Negroes, and the average interval between the two X-ray examinations was 14.2 months.

Twenty-five cases of tuberculosis developed, an incidence rate of 2.4 per thousand per year. The average age at the time tuberculosis was discovered was 32.5 years, and more than two-thirds of the cases occurred in individuals over thirty years of age.

Study of a sample of over 4,000 individuals who failed to return for a second X-ray examination did not indicate that the rate of development of tuberculosis in this latter group was appreciably higher than in those who did return.

Comparison of the annual incidence rates in the predominantly Negro home-relief population of Harlem with the rates in white groups of higher economic level did not reveal any marked differences.

This study has led to the conclusion that the annual incidence rate is not determined by the mortality rate. Incidence and mortality are independent of each other and their resultant is the prevalence. Attempts to link these three factors through the application of rigid artificial formulae only lead to confusing and contradictory results.

SUMARIO

Determinóse la frecuencia de la tuberculosis en la población adulta aparentemente sana de la zona de Harlem, en la ciudad de Nueva York, radiografiando de nuevo a un grupo de personas socorridas del erario público, cuyas películas anteriores no habían revelado signos de tuberculosis pulmonar. El grupo comprendía 8,731 personas, 86.2% de las cuales eran negros, y el intervalo entre las dos radiografías promedió 14.2 meses.

Entretanto se habían presentado en el grupo 25 casos de tuberculosis, o sea un coeficiente anual de 2.4 por mil. Para la fecha en que se descubrió la tuberculosis la edad media era de 32.5 años y más de las dos terceras partes de los casos presentáronse en individuos de más de 30 años.

El estudio de una muestra representativa de más de 4,000 individuos que no regresaron para la segunda radiografía no indicó que la frecuencia de la tuberculosis en el segundo grupo fuera apreciablemente mayor que entre los que volvieron para examen.

Una comparación de los coeficientes anuales de tuberculosis entre la pobla-

ción de Harlem en que predominan los negros asistidos del erario público y entre los grupos blancos en mejor situación económica, no reveló mayores diferencias.

Este estudio condujo a la deducción de que el coeficiente de morbidad anual no es determinado por el coeficiente de mortalidad, siendo ambos independientes y la frecuencia el resultado de ambos factores. Los esfuerzos realizados para enlazar esos tres factores mediante la aplicación de rígidas fórmulas artificiales culminan invariablemente en resultados confusos y contradictorios.

The author is greatly indebted to Miss Jean Downes of the Milbank Memorial Fund for her advice and assistance in the preparation and analysis of this material.

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DISCUSSION

Dr. Ada Chree Reid, New York: We have been particularly interested at the Metropolitan Life Insurance Company in this problem that Doctor Robins has just presented to you because, despite careful preëmployment examination, including fluoroscopy and radiography, and despite vigilant observation of our employees, we still have a few cases of pulmonary tuberculosis developing each year; for the ten-year period 1930 to 1939 inclusive, we had 330 such cases. It is true that our incidence has dropped from 50 cases in 1930 (4 per 1,000 employees) at which time our Tuberculosis Control Program was just getting under way, to 10 cases in 1941 (0.7 per 1,000 employees), so that we feel our Program is functioning well, but we seem to be unable to reduce the incidence of new cases beyond this point.

We do not have an X-ray film of each employee each year, but a fluoroscopic examination is always carried out, and while we recognize a source of error in fluoroscopy, in our experience it is so small that we are certain only a rare case of pulmonary tuberculosis is missed. Therefore, while our figures are not exactly comparable to those of Doctor Robins which are based on two consecutive yearly X-ray surveys, nevertheless, we feel that a comparison of our figures with his is of some value.

We do not find, in our 330 cases, that sex influenced the incidence rate of the entire group to any significant degree, but that sex did influence the incidence rate at the various ages. Females represent 75.8 per cent of the population and account for 79.3 per cent of the clinically significant cases of pulmonary tuberculosis, the proportion of the cases being highest in the twenty to twenty-four age period, in which the females represent 32.1 per cent of the population, but account for 44.6 per cent of the tuberculosis. At age forty and over we have the same number of male and female clerical employees, but the males produce 3.3 per cent of the cases, while the females produce 1.8 per cent which is a rate of

1.4 per 1,000 males and 0.8 per 1,000 females. Doctor Robins reports that two-thirds of all his cases developed in individuals over age thirty. In our series, we had only 70 cases, 40 males and 30 females, or about one-fifth of the total developing in employees over thirty.

Our experience with respect to history of contact and absence of symptoms is similar to that of Doctor Robins. Very few of our tuberculous cases (3 per cent) gave a history of significant contact and only about one-third had symptoms prior to the discovery of their disease.

Of these 330 cases, 69 had had previously negative roentgenograms; in 8 instances less than six months and in 9, a year or less previous to the film which revealed the disease.

I believe that studies such as this report by Doctor Robins have a double significance, first because only by such repeated surveys of the same group can the true prevalence rate of pulmonary tuberculosis be found, and also because these studies reveal the necessity of subsequent check-up examinations of an apparently healthy group and the hazard of that false sense of security which a single survey of a group produces.

As a practical and present-day problem the results of this study have a very significant implication in the medical follow-up of our military forces and suggest that subsequent X-ray films after induction into the service, as well as before induction, are indicated.

DISAPPEARANCE OF TUBERCULIN REACTION IN CHILDREN UNDER TREATMENT FOR ALLERGIES[1,2]

F. M. POTTENGER, JR. AND F. M. POTTENGER

PRODUCTION OF SENSITIZATION

When tubercle bacilli gain entrance to the human body in numbers sufficient to establish an infection, certain things happen. A focus is established at the site of implantation and in the lymph nodes which drain the area. The number of bacilli which cause this first or primary focus is small, and the host's natural physiological defense is usually able to localize them. They rarely find their way beyond the regional lymph node or nodes in sufficient numbers to cause infection in other organs. Primary infection is not only localized but its activity nearly always ceases without producing symptoms of disease.

However, when infection occurs, bacillary products escape from the primary focus into the blood stream and produce sensitization of the body tissues to bacilli and bacillary proteins; and subsequent inoculations are met by an increased resistance. This increased competency to resist is shown by the tissues reacting more quickly and more energetically. They react with inflammation and exudation and various antibacillary effects. The monocytes respond more quickly in the formation of epithelioid cells and in the production of protective tubercle.

ALLERGY THE BASIS OF THE TUBERCULIN TEST

The inflammatory portion of the protective reaction which occurs when bacillary protein again contacts the tissues of one who has been previously infected is termed "allergy." Allergy is what we attempt to detect by the local tuberculin test. It is the portion of the many-phased immunity mechanims which is easiest to detect because it is inflammatory and is present in the cutaneous tissues. Furthermore, it appears soon after infection has taken place. One particular part in immunity played by this inflammatory reaction is the fixing and anchoring of bacilli and bacillary products by which their ready passage through the tissues is prevented.

It is an antigen-antibody reaction and takes place whether the bacilli or bacillary proteins come from a new invasion from without, a metastatic spread from within, or is due to bringing tuberculo-protein in direct contact with the cells as in the various tuberculin tests.

STABILITY AND LABILITY OF ALLERGY

When the tissue cells have once been rendered allergic their reaction to bacillary protein is more or less permanent, although it is somewhat labile as will

[1] From the Pottenger Sanatorium and Clinic, Monrovia, California.

[2] Read at the annual meeting of the California Tuberculosis Association and the California Trudeau Society, Los Angeles, April 9, 10 and 11, 1942.

appear from our observations, varying under different conditions and at different times. This same lability underlies other allergies, both bacterial and nonbacterial. This lability does not seem to be sufficiently recognized. When antigen-antibody reaction takes place on the surface of cells, it may be very energetic; but when an excess of antibody is thrown off from the cells into the circulation, and when the tissues have developed other phases of immunity, the same bacteria or foreign protein, on again entering the tissues, may be destroyed by circulating antibodies and the reaction at the cell's surface may accordingly become less marked. In some instances it may not appear at all, as in diphtheria where the circulating antibodies alone are the main defensive force and, of themselves, are sufficient to overcome the disease.

In tuberculous disease, which must be considered as a succession of reinoculations of tubercle bacilli, the individual develops other phases of immunity such as an increased phagocytosis, a greater ability to inhibit the growth and development of bacilli and a greater ability to destroy bacilli.

In clinical tuberculosis the patient's ability to withstand larger and larger reinoculations with a decreased local inflammatory reaction is necessary if the patient is to live. In other words, desensitization is a necessity and takes place as immunity increases. Otherwise, no patient could withstand advanced tuberculosis. This is important not only in clinical tuberculosis but in understanding the tuberculin reaction. It explains the fact that a patient who has developed a chronic proliferative tuberculosis may show a very mild reaction to tuberculin, which, when properly interpreted, means that, as other phases of a more efficient immunity develop, sensitization decreases.

ANTIGEN-ANTIBODY REACTION THE NORMAL DIGESTIVE PROCESS OF UNICELLULAR ORGANISMS

To understand the inflammatory reaction of allergy we must understand the intracellular digestion of unicellular organisms. Their food is digested within their bodies, while the more complex organisms are provided with a digestive tube where digestion is supposed to wholly take place preparatory to its assimilation. However, the individual cells which make up the complex organism also possess the power of digestion, the same as the unicellular organisms. This is necessary for their protection, for often undigested protein gains access to the tissues; and bacterial infections always throw out protein from within. Enzymes are responsible for the digestion in both instances. It is the cellular digestion which is evident in the tuberculin reaction. Cellular digestion is less necessary if humoral protection is competent.

In discussing allergies we can practically elminate from consideration substances other than proteins. Whenever bacteria or proteins of large molecular size enter the tissues the cells are obliged to digest it in order to save themselves from injury. They take care of small amounts within their normal enzyme production; but if large quantities come in contact with them they must produce larger quantities of enzymes and react more energetically.

CONDITIONS UNDER WHICH A POSITIVE TUBERCULIN TEST MAY BECOME NEGATIVE

The tuberculin reaction may be temporarily depressed or disappear during certain acute infections, such as measles, diphtheria and influenza; or it may disappear should the patient become cachetic, or if he suffers from advanced tuberculosis and is rapidly approaching death. Immunity as a whole is lowered under these conditions.

However, under conditions of health, while the tuberculin reaction may differ in strength from time to time, it is almost the universal belief that it rarely disappears entirely. So persistent is it that, should it be seen to disappear frequently under any given set of conditions, we have the right to suspect that there is a direct relationship between those particular conditions and the disappearance of the reaction; and should the patient maintain a satisfactory degree of health when or after it has disappeared, we would be obliged to accept the conditions as probably favorable to the patient. The reaction has been known to disappear in a few instances when healing of clinical tuberculosis has occurred.

The disappearance of the tuberculin reaction or the lessening of its strength may be due either to the setting aside of immunity, or to a greater competency of the noninflammatory phases and a corresponding reduction in specific sensitization. When it occurs during the acute infectious diseases or in the final stages of tuberculosis it is probably due to a lowering of immunity; while in chronic proliferative tuberculosis, and in cases which have healed or in which it disappears when the patient is in excellent condition, it is probably due to an increased immunity. In the instances which we are now reporting we believe that the decreased sensitization is associated with a greater resistance.

PRESENT OBSERVATIONS

In this paper we wish to report on a group of 41 children whose tuberculin reactions changed from positive to negative while under treatment for conditions other than tuberculosis. The number of cases is sufficiently large to eliminate any accidental relationship. All the patients in this report showed a positive tuberculin reaction to the first dose of PPD at the beginning of treatment and, while under treatment, failed to react to a subsequent dose of the same amount, and in some instances to the second dose of PPD. There was one case in which the reaction became negative and again became positive, showing a marked lability in the reaction. We report no case as positive which showed an erythema and induration of less than 0.5 cm. in diameter.

Most of these patients were being treated for bronchial asthma, hay-fever and chronic bronchitis. In a few the particular complaint was low energy and delayed development.

In our allergic patients we laid no stress on individual sensitiveness and gave no tests to determine to what substances they were sensitized. Most of the allergic cases, however, had been subjected to many tests and were reported as suffering from multiple sensitization. All patients were put on a general regimen

TABLE 1

Tuberculin Tests

CASE NUMBER	DATE	PPD NUMBER	REACTION IN CM.	CASE NUMBER	DATE	PPD NUMBER	REACTION IN CM.
10722	1-15-36	1	1.75	11151	5-19-38	1	1.5
	7- 7-36	1	2.0		5- 1-39	1	0.0
	1- 9-37	2	6x7.5				
	9- 1-37	2	4.5	11096	4- 1-38	2	0.5
	12-27-37	1	1.0		9-28-38	1	0.0
	4-11-38	2	10.0				
	1-30-39	1	3.0	11168	6-28-38	1	0.8
	9-15-41	1	0.0		6-17-39	1	0.5
					12-28-39	1	0.0
10656	9-19-35	1	2.0				
	6-30-37	2	10.0	11291	2- 9-39	1	2.5
	11-29-38	2	0.0		8- 7-39	1	0.0
11238	7-19-39	1	0.3	11500	9-12-39	1	0.5
	12-28-39	1	0.0		7-14-41	1	0.0
					3- 9-42	2	0.0
11036	10-13-37	1	1.0				
	7-14-38	1	0.0	11508	9-18-39	1	0.8
					4-12-40	1	0.0
11112	2-17-37	1	1.5				
	11- 9-39	1	0.0	11737	6-17-41	1	4.0
					1- 6-42	1	0.0
10874	11- 4-36	1	0.7		1- 8-42	2	0.0
	8-21-37	2	0.0				
				10550	12-26-34	1	0.8
11032	9-27-37	1	0.5		12-23-35	1	0.0
	5- 2-38	1	0.5				
	9-21-40	2	0.0	10993	7-21-37	1	0.7
					7-18-38	2	0.0
11090	1-20-38	1	0.8				
	6-27-38	1	1.0	11109	3- 4-38	1	1.5
	1- 6-40	1	0.0		1-26-39	1	0.0
					3-18-40	1	0.0
11700	12-17-40	1	1.5				
	7-14-41	1	0.0	11218	9-29-38	1	5.0
					6-18-41	1	0.0
11194	9- 9-39	1	1.0	11264	1- 6-40	1	2.0
	4- 8-40	1	0.0		12-30-40	1	0.0
11195	9- 9-39	1	1.5	11274	1-11-39	1	1.5
	4- 8-40	1	0.0		2-17-40	1	0.0
11230	11-14-38	1	0.8	11324	4- 7-39	1	0.5
	10-30-39	1	0.0		10-12-40	1	1.0
					4-19-41	1	0.0
11149	5-15-38	1	4.0				
	12- 3-38	1	0.0	11507	6-24-40	1	0.5
					11-30-40	1	0.0

TABLE 1—*Continued*

CASE NUMBER	DATE	PPD NUMBER	REACTION IN CM.	CASE NUMBER	DATE	PPD NUMBER	REACTION IN CM.
11514	10- 3-40	1	3.4	11731	5-13-41	1	1.0
	10- 3-41	1	0.0		12-29-41	1	0.0
11528	2-21-40	1	0.8				
	11- 6-40	1	0.0	10694	6-28-36	1	3.0
					1- 6-40	1	1.4
11548	4-13-40	1	1.0		2-22-42	1	0.0
	11-23-40	1	0.0		3-15-42	2	3.0
11553	5- 9-40	1	2.0	11138	4-21-38	1	1.0
	11-23-40	1	0.0		10-17-38	2	0.0
11570	7-18-40	1	8.0	10856	10- 6-36	1	0.5
	9-17-40	1	0.0		9- 6-38	1	0.0
11576	8-15-40	1	1.5	10440	3-19-34	1	2.5
	2-22-41	1	0.0		3-21-34	1	1.0
					8-26-35	1	0.0
11708	1-31-41	1	1.5		3-24-36	2	0.0
	7-28-41	1	0.0		3-26-36	2	0.0
					8-31-38	2	0.0
11710	2- 1-41	1	2.5		9-2-39	1	0.0
	5-10-41	1	0.0		11-24-39	2	0.0
11729	5-13-41	1	1.0				
	10-25-41	1	0.0				

consisting of a diet rich in protein and animal fats and relatively low in carbohydrates. Aside from using the muscle meats common in the ordinary diet, brains, heart, tripe, kidneys, sweet-breads and liver were used in the proportion of about one to three.

Vitamins for the most part were obtained from natural foods. We used in our diet a special bread made from sprouted rye and wheat, raw liver, the highest grade of raw milk obtainable and vegetable salads. We also used sunbaths. We supplemented the vitamins in our regular diet only by rice molasses, malt and sometimes codliver oil. The diet is much the same as that served to the inpatients of the Pottenger Sanatorium. Considered in its protein, fat and carbohydrate content it is roughly a one-one-one diet. These children were also given regulated exercises. As a part of their treatment each child was given a potent extract made from the adrenal cortex.

COMMENT

Sensitivity of tissues to allergens and resistance against infections have long been considered by students of constitution as being affected by permeability. The more permeable the tissues the more subject the patient to allergies and infections.

This recently has been emphasized by Lurie (1) in his study of tuberculosis in rabbits whose heredity was carefully controlled. He demonstrated that the less permeable the tissues of a given group of rabbits, the more resistant they were to tuberculous infection. Furthermore, the allergic inflammatory reaction in chronic tuberculosis is much less prominent in the less permeable proliferative form of the disease. It is also known that proliferative tissue is more resistant to metastases.

Furthermore, there is evidence which is at least suggestive that nutrition plays a part in the permeability of tissues. We know it plays a part in resistance to infection. Weather changes (2) which bring about increased metabolic activity and increased permeability of tissues stimulate those tissues especially which are sensitive to infection and allergens and are known to reactivate tuberculosis and to precipitate allergic paroxysms.

That permeability is a very important factor in the allergic diseases is recognized in asthma where there is a markedly increased permeability of the blood vessels and other structures of the bronchi. In hay-fever and occular allergies there is an increased permeability of the nasal and conjunctival tissues. The relief of these allergies may be brought about by those substances or those measures which will reduce permeability and decrease the exudative phenomena. Adrenalin acts quickly as a vasoconstrictor and relaxes the bronchial musculature in asthma when used subcutaneously, and in nasal and occular allergies it reduces permeability of the tissues when used locally. The adrenal cortex also reduces permeability, but more slowly, and produces a more continuous effect. Calcium has a similar effect but acts more slowly than adrenalin. There are numerous other measures which might be advantageously used that act in a similar way.

In these children in whom the allergic phenomena were lessened to such an extent that they failed to react on the repetition of the first dose of PPD, and some to the second dose of PPD, we must assume that the effect must have been brought about by improving the patient's physiological mechanism, which was probably done by changing his chemical and physical tissue reactions. It is probable that had a larger amount of tuberculin been used in the injection, a reaction might have been brought about, but of this we are not certain because it was not tried.

The analysis of these cases indicates that the tuberculin reaction (allergic) is not as stable as we had thought, and that changes in its stability are brought about under various circumstances. This may be important in explaining the fact that a certain proportion of people who do not react to the first dose of PPD will react to the second dose of PPD. It is probable, too, that the time when the dose is given is important in the reaction. An individual might react to-day and might not react under different circumstances at another time. Or he might not react to-day and might react at another time. We meet this variability in the therapeutic use of tuberculin.

Not only our experience but the experience of others has shown that the

adrenal cortex produces substances which have an antiallergic effect (3, 4). That the diet increases resistance has long been known.

That the immunity mechanism varies with diet has further been shown in vaccinating cattle against infectious abortion. By giving two doses of vaccine—one soon after birth, and the other several months later—the animals thereafter are protected against abortion. Under usual conditions of feeding the blood will fail to react, but when the animals are put on green pasture rich in vitamins it has been shown that a sufficient increase of antibodies appears in the blood to cause the sera that was previously negative to agglutinate with a high titre (5).

In discussing any phase of resistance to infection it is necessary to understand that resistance is physiological and that immunity is an exaggeration of the normal physiological mechanism. We believe that both diet and the adrenal cortex (6, 7) were probably factors in the phenomena herein reported.

We have discussed immunity as a labile mechanism and wish to emphasize that the tuberculin reaction as a part of that mechanism is likewise subject to changes in intensity.

SUMMARY

1. The tuberculin reaction is a part of the immunity mechanism. It is an exaggeration of the normal ability of cells to protect themselves by the destruction of bacillary protein.

2. The tuberculin reaction is not a stable mechanism, but decreases in intensity and may even disappear under conditions of increased immunity, and also when the immunity mechanism fails.

3. In discussing any phase of resistance to infection it is necessary to understand that resistance is physiological, and that immunity is an exaggeration of normal physiological activity.

4. A report is made of 42 children whose tuberculin reactions disappeared while being treated for allergies, low energy and delayed development. Special measures used in treatment were: (*1*) a potent extract of the adrenal cortex; (*2*) a high protein, high fat and low carbohydrate diet. In the preparation of foods special attention was given to the protection of their vitamin content.

SUMARIO

1. La reacción a la tuberculina constituye parte del mecanismo de inmunidad, siendo una exageración de la capacidad normal de las células para protegerse mediante la destrucción de la proteína bacilar.

2. La reacción a la tuberculina no constituye un mecanismo estable, pues disminuye en intensidad y hasta puede desaparecer en condiciones de mayor inmunidad y también cuando fracasa el mecanismo de inmunidad.

3. Al discutir cualquier fase de resistencia a la infección, es necesario comprender que la resistencia es fisiológica, y la inmunidad una exageración de la actividad fisiológica normal.

4. Preséntase un informe relativo a 42 niños cuyas reacciones a la tuberculina

desaparecieron mientras se les trataba por estados alérgicos, falta de energía y atrofia. Las medidas especiales utilizadas en el tratamiento fueron: (1) un extracto potente de corteza adrenal; (2) un régimen alimenticio rico en proteína y grasa y bajo en carbohidratos de carbono. En la preparación de los alimentos se concedió atención especial a resguardar el contenido de vitaminas.

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TUBERCULIN SENSITIVITY AND THE DEVELOPMENT OF TUBERCULOSIS IN NURSES[1]

SPENCER SCHWARTZ

This study consists of an analysis of the sensitivity to tuberculin and a report on the later history of 270 nurses who were affiliated at the Trudeau Sanatorium from 1936 to September, 1941. Thus the follow-up period was from six months to six years.

The chests of these nurses were X-rayed when they arrived at the Sanatorium and again just before leaving. Tuberculin tests were done, using Old Tuberculin supplied by the Saranac Laboratory for the Study of Tuberculosis. This was given intracutaneously, beginning with a dose of 0.001 mg. If a positive reaction was not obtained, the dose of tuberculin was increased tenfold at two to three day intervals, until a dose of 10 mg. had been given. The sites of injection were examined twenty-four hours and forty-eight hours after testing; the size of the areas of erythema and oedema, if present, were recorded. For the reaction to be considered positive, it was required that there be an area of oedema of over 5 mm. in diameter, accompanied by erythema and persisting for forty-eight hours (6).[2]

There were 234 affiliating student nurses, twenty to twenty-one years of age, who had completed one and one-half to two years of their training. They came from several hospitals in up-state New York. While these institutions had no tuberculosis services, they occasionally admitted tuberculous patients. These nurses remained at the Sanatorium for two months. The thirty-six remaining nurses were graduate nurses ranging in age from twenty-five to forty years. Their period of postgraduate training at the Sanatorium lasted four months.

It was found that the incidence of tuberculous infection, the sensitivity to tuberculin and the reaction to parenchymal pulmonary tuberculosis, when present, was quite different in the two groups.

On arrival at the Sanatorium, 179, or 77 per cent, of the 234 affiliating students had positive tuberculin reactions and the chest X-ray films of 6 of them showed the presence of parenchymal tuberculosis. It has already been shown that the use of large doses of tuberculoprotein will result in a much greater proportion of positive reactions in persons without other evidence of tuberculous infection than will occur with the dosage in general use (7). It would be

[1] From Trudeau Sanatorium, Trudeau, New York.

[2] A little more than one-half of those who were considered to have negative tuberculin reactions to the 10 mg. dose had what might have been classified as questionably positive reactions (6). However, since the dose used was so strong, it was felt that some of these questionable reactions might have been due, at least partially, to proteins in the tuberculin other than the tuberculo-protein, even though it must be admitted that the usual reaction to intracutaneous injection of foreign protein is quite different from a tuberculin reaction. In any event, the fact that the subsequent behavior of the negative reactors and those who might have been called questionably positive was essentially the same in all respects seemed to justify their having been placed in the same category.

supposed, therefore, that the use of a dose of 10 mg. of Old Tuberculin would produce a larger percentage of positive reactions than might ordinarily have been expected in nurses half way through their training, and without having worked on a tuberculosis service. In a recent study of female normal school students in up-state New York, between 24 and 27 per cent were found to be positive to tuberculin (13). This frequency of infection was much nearer that of approximately 25 per cent found in the middle west in college students and nurses on entering training (2, 10, 11, 16) than that of 55 to 57 per cent found in New York and Boston (1, 4, 14). Since most of the young women in the present group came from rural communities or small cities in up-state New York, comparison could be made with studies done in the middle west on nurses before beginning work on tuberculosis wards (2), or on graduation without having done such work (8). Between 40 and 50 per cent of these nurses were found to have positive reactions to 1 mg. of tuberculin. In the present study, if a dose of 1 mg. had been the greatest used, only 50 per cent of the reactions would have been positive instead of 77 per cent, as noted above.

In the 6 student nurses who had pulmonary tuberculosis on arrival at the Sanatorium, the lesions were minimal in extent and inactive in appearance. Three of them had had a period of sanatorium treatment previously, and these 3 have remained well. The others had no knowledge of the presence of their disease. All of them relapsed within a year. Each was given sanatorium treatment and has remained well subsequently. In this group, at least, there seemed to have been value in a period of treatment to attain stabilization of the lesion.

All of the group of 36 graduate nurses had positive tuberculin reactions on arrival at the Sanatorium, and the chest X-ray films of 10 of them showed the presence of parenchymal pulmonary tuberculosis. Since 90 to 95 per cent of graduate nurses have been found to have positive tuberculin reactions (4, 14), it was not surprising that all of this small group reacted positively. Relatively little has been written concerning the tuberculosis morbidity among nurses during the years after graduation, since it has not been customary in the past to subject these women to routine examinations. In one study, pulmonary tuberculosis apparently was found in about 5 per cent of a group of 225 private duty nurses in Indianapolis (17). In any event the incidence of parenchymal disease in the present group was inordinately high. However, it should be noted that all of these women were aware of the presence of their disease; in fact 9 of the 10 had previously had sanatorium treatment. It was to be expected that they above all others would be interested in special training to better fit themselves for the care of the tuberculous. Thus, it seemed reasonable to believe that the special attraction that a postgraduate course in tuberculosis nursing offered to tuberculous nurses accounted for the presence of so large a proportion of tuberculosis morbidity in this group.

The later history of these 10 graduate nurses who had parenchymal lesions is encouraging, in that 9 of them have remained well and have continued to work. One suffered a slight increase of disease, but this cleared after a few months of treatment. She has remained well and has been working since that time.

Of the total of 234 affiliating students, 228 showed no evidence of parenchymal disease. Of these, 173, or 75 per cent, were positive to tuberculin. Also, 26 of the 36 graduates showed no evidence of disease and all of these had positive reactions. As has just been pointed out, these findings were not remarkable. However, when the degree of sensitivity to tuberculin of the reactors was tabulated, a further difference in the two groups was noted (table 1). Among the affiliating students only 50 per cent of the reactors were positive to 0.1 mg. or less, while 34 per cent required a dose of 10 mg. to produce a reaction. On the other hand, 77 per cent of the graduates reacted to 0.1 mm. or less and 4 per cent only to 10 mg.

Thus the degree of sensitivity of the graduate nurses was greater than that of the students, but was somewhat less than that of a group of tuberculous patients who had been tested previously. That the sensitivity to tuberculin was greater among persons suffering from clinical tuberculosis than in those without evidence of disease, was not remarkable, but the fact that the sensitivity of graduate nurses was considerably greater than that of the student nurses was of interest

TABLE 1

Amount of tuberculin necessary to produce a reaction

DOSE	173 STUDENT NURSES	26 GRADUATE NURSES	238 TUBERCULOUS PATIENTS (15)
mg.	*per cent*	*per cent*	*per cent*
0.001	5	8	53
0.01	28	38	41
0.1	17	31	5
1.0	16	19	1
10.0	34	4	0

and could not be entirely explained. A partial explanation may have been that their greater age, and in consequence a greater opportunity for repeated superinfection, had resulted in their maintaining a higher degree of allergy.

Retesting of the student nurses upon completion of their two months' course of affiliation showed that 13, or 25 per cent, of the 55 who had had negative reactions now had positive ones. Stated in another way, that comparison may be made with other studies of this subject, the reactors increased from 77 to 81 per cent. This finding was in agreement with that of others who found that 25 per cent of the negatively reacting nurses became positive after twelve weeks of caring for tuberculous patients, and that 15 per cent became positive after six weeks of such work (8). Another author showed an increase of positive reactors from 46 to 68 per cent under similar circumstances (2). However, strict comparison of this with the findings in the present report was considered difficult because of the difference in the proportion of the original reactors.

The dose of tuberculin necessary to produce a reaction in those who had been negative varied from 0.000,1 to 1.0 mg. One student nurse, who on retesting was positive to a dose of 0.001 mg., was found to have had low-grade fever and

cough for the preceding two weeks, and an X-ray film taken soon after showed that a tuberculous lesion had developed in the lung. The other 12 who became positive had no accompanying symptoms or changes in their X-ray films, although sensitivity to tuberculin developed to a comparable degree in 6 of them. The remainder required a dose of 0.1 mg. or more to produce a reaction.

During the first portion of this study, the original reactors were not retested with tuberculin on leaving the Sanatorium. In 92 of those who were retested, it was found that the degree of sensitivity to tuberculin remained the same in 60 per cent. It was considered to be less in 10 per cent (those requiring ten times the original dose to produce a reaction), and greater in 30 per cent (those requiring $\frac{1}{10000}$ to $\frac{1}{10}$ the original dose to produce a positive reaction). This proportion remained about the same, regardless of whether the original reacting dose had been large or small. Marked changes in sensitivity were relatively infrequent. Eighteen required $\frac{1}{10}$, 5 $\frac{1}{100}$, 3 $\frac{1}{1000}$ and 2 $\frac{1}{10000}$ the original dose to produce a reaction. An X-ray film taken a day before the final tuberculin test of one of the young women who needed only $\frac{1}{10000}$ of the previous dose to cause reaction, showed the development of a pulmonary lesion, which was accompanied by symptoms consisting of low-grade fever and malaise. This was the only instance of the development of symptoms or a demonstrable lesion. In fact, the rest of the 92 nurses who were retested on leaving the Sanatorium have remained well. It would seem that in this group it was the exception rather than the rule for changes in sensitivity to tuberculin to be accompanied by evidence of the development of disease.

Up to the present time, 2 of the 55 student nurses who were negative to tuberculin on arrival at the Sanatorium have developed parenchymal disease; a morbidity of 3.6 per cent. In addition, 4 of those originally positive to tuberculin have developed lesions; a morbidity of 2.3 per cent. The greater morbidity among the student nurses that were originally negative to tuberculin was to be expected, as has been shown by Heimbeck (9) and many others (1, 4, 14). However, inspection of the dosage necessary to produce a reaction in the 4 student nurses, originally positive to tuberculin, who later developed disease, showed that 3 of them had required 10 mg. and one, 1 mg. before a reaction was obtained. In marked contrast to this, all of those who had reacted to smaller doses have remained well. The problem as to whether or not the degree of the tuberculin sensitiveness of an individual influences his resistance to superinfection, has been of interest since the discovery of tuberculin. While no general conclusions may be drawn regarding this matter, it would seem that, in the small group under consideration, the presence of slight tuberculin sensitiveness provided less protection than when this was present to a more marked degree.

It has been shown that only a slight morbidity, and essentially no mortality from tuberculosis should be present among student nurses if a proper case-finding program has been used (3, 5). It is, therefore, a cause for some satisfaction to find that none of the lesions in the 6 who developed disease has progressed beyond the minimal stage, and that 4 of them have regained their health and returned to work.

Opinions as to the relative danger of work on a tuberculosis service as compared with work elsewhere in a hospital have not been in agreement. The development of primary infection in a group of Bellevue student nurses was found to be no more often related to the tuberculosis service than to other services (14). In contradistinction to this, from a study of the student nurses in several hospitals in Minneapolis, it was concluded that considerably more infection occurred on the tuberculosis services (8). The question as to how many of the 6 young women in the present group acquired, while at the Sanatorium, the infection which later developed into parenchymal lesions could not be answered. In one, whose tuberculin test was negative on arrival and positive on leaving, and whose X-ray film showed the development of a lesion a month later, there seemed to be definite relationship between work in the Sanatorium and development of disease. However, in another, with a history of exposure a few weeks before a positive tuberculin test on arrival, and an X-ray film, which, though negative at first, showed the presence of a lesion seven weeks later, there was some doubt as to whether the previous exposure might not have been at least partially responsible for her disease. The remaining 4 did not develop lesions until more than a year after leaving the Sanatorium, and 2 of them were known to have had additional exposure during this later period.

In spite of the inability to find definite correlation between affiliation at the Sanatorium and development of disease, the fact that 25 per cent of the student nurses who were negative to tuberculin became positive by the time their course was completed, indicated that primary infection was occurring in some of them, and that the whole group was coming into contact with tubercle bacilli. This occurred in spite of the fact that the student nurses were required to wear masks while on duty and repeatedly were instructed as to personal cleanliness. In addition, the patients they cared for were almost all quite coöperative about observing proper precautions as to cough and disposal of sputum.

Replies by 68 tuberculosis sanatoria to a questionnaire indicated that two-thirds of them were using a modified isolation technique and the remainder a strict isolation technique. Unfortunately, due to lack of appropriate data, it could not be determined whether or not the use of the strict technique was accompanied by evidence of less infection among the nurses (12). While it would seem on superficial examination that the use of a strict technique in caring for tuberculous patients might offer the solution to this problem, further consideration suggests that the rigid enforcement of such a procedure would be difficult and occasionally impracticable. This would be particularly true in institutions caring for ambulant patients. Nevertheless, as strict a technique as may be possible under the circumstances should be followed.

Attention to other factors should not be forgotten. Instruction of tuberculous patients as to proper care in coughing and disposing of sputum is perhaps more important than any other single measure. A search for unsuspected tuberculosis by routine chest X-ray films and sputum examinations should be made of patients admitted to hospitals. In addition, a case-finding program for hospital employees other than nurses will benefit both the employees and the nurses.

Proper food, good living conditions, and moderate hours of work, while not lessening infection, at least should increase the individual's resistance to disease. Finally, a thorough case-finding program, including the frequent use of tuberculin tests and carefully interpreted chest X-ray films, should be followed through to its natural conclusion by insisting upon an adequate period of treatment for all those showing evidence of disease.

SUMMARY

1. In 270 affiliating graduate and student nurses, the degree of sensitivity to Old Tuberculin was found to be greater among the graduate nurses than among the students.

2. On arrival, all graduate nurses and 77 per cent of the students were found to be positive to 10 mg. or less of tuberculin.

3. Twenty-five per cent of the non-reacting student nurses became positive by the time their course of affiliation was completed.

4. One of the 10 graduate, and 3 of the 6 student nurses having pulmonary tuberculosis on arrival at the Sanatorium, have relapsed. Lack of a previous period of treatment seemed to be the chief factor coincident with relapse among the students.

5. None of the graduate nurses, 3.6 per cent of the tuberculin-negative, and 2.3 per cent of the tuberculin-positive student nurses who had no demonstrable pulmonary disease later developed pulmonary tuberculosis. The reactors that developed lesions were originally relatively insensitive to tuberculin.

6. Suggestions to aid in reducing tuberculous infection and morbidity among nurses are given.

SUMARIO

1. Entre 270 enfermeras recibidas y estudiantes de enfermera la sensibilidad a la tuberculina antigua resultó mayor entre las primeras que entre las segundas.

2. A su ingreso, todas las enfermeras recibidas y 77% de las estudiantes resultaron positivas a 10 mg o menos de tuberculina.

3. Un 25% de las estudiantes negativas a su ingreso, se volvieron positivas para la fecha en que completaron su curso de afiliación.

4. Una de las 10 enfermeras recibidas y 3 de las 6 estudiantes que tenían tuberculosis pulmonar a su llegada al sanatorio han experimentado recidivas. La falta de un período previo de tratamiento pareció ser el principal factor en las recidivas en las estudiantes.

5. Manifestaron después tuberculosis pulmonar 3.6% de las estudiantes negativas y 2.3% de las positivas a la tuberculina que no tenían neumopatía observable, pero no sucedió esto con ninguna de las enfermeras indemnes a su ingreso. Las reactoras que manifestaron después lesiones, eran al principio relativamente insensibles a la tuberculina.

6. Ofrécense indicaciones para ayudar a disminuir la infección y morbidad tuberculosa en las enfermeras.

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TREATMENT OF TUBERCULOSIS WITH PROMIN[1,2]

A Progress Report

H. CORWIN HINSHAW, KARL PFUETZE AND WILLIAM H. FELDMAN

The clinical trial of promin for treatment of pulmonary tuberculosis appeared advisable when adequate evidence had accumulated to demonstrate that promin produced definite inhibition of experimental tuberculosis (1) and when apparently adequate information was available to indicate that the compound was tolerated reasonably well by human beings (2, 3). The clinical phase of our studies on chemotherapy of tuberculosis was started in March, 1941.[3] It seems appropriate to describe briefly the observations which we have made during this first year of study.

The toxicity of the compound exceeded earlier expectations which were based on experience with short periods of therapy for acute diseases by parenteral routes of administration. The nature of the disease, tuberculosis, necessitated prolonged treatment, and the parenteral methods of administration soon were discarded in favor of the oral route. The parenteral injections required were numerous and painful and the drug was excreted rapidly when so administered. Oral administration yielded more sustained blood levels of the drug. The oral route was preferred also because of our desire to follow as closely as possible the procedure which yielded successful results in guinea pigs. However, the drug is definitely more toxic for the human species than it is for the guinea pig when given orally. This greater toxicity permitted us to use only a twentieth to a fiftieth of the dose per kilogram of body weight. The blood levels attained in human beings were higher than anticipated, ranging from a fourth to a half as high as in guinea pigs. We have published some notes (2, 4) on the toxic effects of promin when administered orally to man and further studies will be reported. The marked tendency of this drug to produce anaemia is the principal factor which limits dosage and requires meticulous supervision of patients. Fortunately blood regeneration is rapid and occasional interruption of therapy for a week or two is usually sufficient to permit stabilization of the blood picture. The discrepancies noted between parenteral and oral administration have suggested that the compound is altered somehow in the digestive tract, increasing its toxicity and decreasing its rate of excretion. There is no direct evidence to indicate what this chemical change may be, but the drug may be broken down to a substance resembling diamino-diphenyl-sulfone. The latter compound has inhibited tuberculosis successfully in guinea pigs (5) and we have confirmed these results. It has been considered excessively toxic for man (6).

[1] Presented before the Medical Section at the 38th annual meeting of the National Tuberculosis Association, Philadelphia, Pennsylvania, May 8, 1942.

[2] From the Mayo Clinic and Mayo Foundation, Rochester, Minnesota, and from Mineral Springs Sanatorium, Cannon Falls, Minnesota.

[3] Promin was supplied by Dr. E. A. Sharp of Parke, Davis & Company, Detroit.

This report is concerned chiefly with a series of 36 patients, including all patients who received promin treatment with an average daily dose of at least 0.8 g. for four consecutive months or longer. It must be emphasized that most of these patients received therapy intermittently (1.2 to 1.6 g. per day) and the average dose was computed on the basis of total elapsed time including the rest periods. Administration of the drug was discontinued temporarily whenever objective or subjective toxic manifestations made this appear advisable. Dosage was regulated to approach the individual's limit of tolerance. Patients who had minimal lesions or negative sputum are excluded from this study; also those who had extrapulmonary tuberculosis are not included in this group of 36 patients. Patients receiving collapse therapy affecting the lesions under study were also excluded from this group. All were under sanatorium or hospital management

TABLE 1

Tuberculous patients treated with promin (orally)

	PATIENTS
"Adequate" treatment administered (average 0.8 g. or more daily*; 4–12 months)	36
"Inadequate" treatment, because of:	
Toxic manifestations	12
Subjective discomfort	10
Recent cases	9
Terminal cases	4
	35
Excluded because of collapse therapy, negative sputum, extrapulmonary tuberculosis	35
Total treated	106

* Usual dose was 1.2 to 1.6 g. daily in divided doses, with occasional interruptions; average dose computed on basis of total elapsed time.

with partial or complete rest in bed. Table 1 summarizes data on all patients who received treatment.

RESULTS

Tuberculosis is such a protean disease that results are difficult to classify and the cause of observed improvements is exceedingly difficult to ascertain. For purposes of presentation we have classified the 36 patients who received "adequate" therapy into four groups. Group 1 (9 patients) did not show convincing objective signs of improvement. While the sedimentation rate often decreased and subjectively some patients felt better, their lesions were not altered significantly in roentgenographic appearance. Group 2 (8 patients) showed slight but definite evidence of improvement but in no instance was this of striking degree. Group 3 (6 patients) consisted of those whose rapidity and degree of improvement were satisfactory and consistent when judged by all available criteria. Group 4 (8 patients) showed rapid, marked and unexpected improve-

ment which often altered the original prognosis. In one case the lesions extended but later improved. Four patients who received adequate therapy died. One of these had improved.

The rapidity and degree of improvement were judged by objectively demonstrable criteria. No serious consideration was given to the patient's opinion as to his sense of well-being, nor to such nonspecific factors as appetite, weight, cough, expectoration, blood sedimentation rate and so forth. Some patients who were classified as unimproved had improved subjectively and in several instances the blood sedimentation rates had decreased greatly, even among patients whose rates had been consistently high for prolonged periods previous to chemotherapy.

The roentgenological evidence was given greatest weight, and the rapidity of improvement was considered as well as the ultimate degree of improvement in

TABLE 2

Treatment of pulmonary tuberculosis with promin

	TYPES OF CASES TREATED				DIED	WORSE
	Group 1 (no change)	Group 2 (slight improvement)	Group 3 (moderate improvement)	Group 4 (marked improvement)		
Cases (total 36)	9	8	6	8	4	1
Extent of disease:						
Far advanced (total 23 cases)	5 (56%)*	5 (62%)	4 (67%)	5 (62%)	4 (100%)	0
Moderately advanced (total 13 cases)	4	3	2	3	0	1
"Old chronic" fibrocaseous lesions (total 23 cases)	9 (100%)	8 (100%)	2 (33%)	4 (50%)		
Average time in sanatorium before treatment, months	24	16	13	8	1	18

* Percentages in tables 2 and 3 are on the basis of total in each group.

the roentgenographic picture. No patient who failed to improve roentgenologically during the first two months of treatment was classified in either group 3 ("moderate" improvement) or group 4 ("marked" improvement). Rapid improvement could not be anticipated in the large proportion of patients whose lesions were predominantly of long duration, characterized by extensive fibrosis and caseation. It will be noted (table 2) that all patients who showed little or no improvement belonged to this class. Of 23 patients who had such lesions, 6 improved either to a moderate or to a marked degree. In the latter instances, improvement consisted of either closure of cavities or resolution of recent extensions of the disease or both. Cavities were clearly present in 26 of the 36 cases before treatment. After four to twelve months of chemotherapy, apparent closure of one or more cavities was observed in 10 patients, of whom at least 4 had additional cavities which remained open.

Fresh exudative lesions were present in 13 (table 3). In all instances, there was prompt improvement of such lesions, clearly detectable within approximately two months after institution of therapy. The lesions disappeared or assumed an appearance of stability within four to six months. Associated fibrotic lesions in these cases often showed little change during this period. Such infiltration of exudative type frequently disappears rapidly after nonspecific therapy and observation of a larger series of cases would be necessary before chemotherapy could be given credit for the improvement noted in these cases.

TABLE 3

Results of treatment of pulmonary tuberculosis with promin

	NO CHANGE GROUP 1	IMPROVEMENT			DIED	WORSE
		Slight Group 2	Moderate Group 3	Marked Group 4		
Cases	9	8	6	8	4	1
Sputum reversal (39%) (positive to negative)	3 (33%)*	2 (25%)†	3 (50%)‡	6 (75%)§	0	0
Closure of cavity	0	3 (37%)	2 (33%)	5 (62%)	0	0
Clearing of fresh exudative lesions (13 cases)	None present	None present	6	6	1	0
Roentgenological improvement within two months	0	2 (25%)	6 (100%)	8 (100%)	1	0
Average sedimentation rate before treatment (Cutler) (mm.)	20	24	15	29	28	20
Average sedimentation rate after treatment (mm.)	11	13	8	7	32	20
Average daily dose of promin (oral) (g.)	0.99	0.96	0.87	1.03	0.92	0.8
Average length of treatment (days)	156	203	221	223	195	236

Treatment usually intermittent (1.2 to 1.6 g. daily).
* Gastric aspiration negative to culture in 2 cases.
† Gastric aspiration negative to culture in one case.
‡ Gastric aspiration negative to culture in all cases.
§ Gastric aspiration negative to culture in 3 cases.

In all of the 36 cases the sputum was positive before treatment and after four to twelve months of chemotherapy, in 14 cases the sputum has become consistently negative to repeated smears and concentration methods (table 3). Culture of aspirated gastric contents has been negative in 9, while this information is not available in the remaining 5 cases. In a few additional cases the number of tubercle bacilli has been reduced markedly but the bacilli may be detected by either concentration or cultural methods. It should be pointed out that it is possible for tubercle bacilli to live and reproduce within the body of a patient who is receiving maximal doses of this drug. In one instance promin has

been instilled into an open empyema cavity almost daily for more than one year; yet tubercle bacilli are still present in the pus, even though their number is reduced greatly.

A significant decrease of sedimentation rate following treatment with promin was observed frequently (table 3) even when other objective tests failed to indicate improvement. This test was not considered in judging improvement because of its nonspecific character. However, it is of interest to note that in this series, if fatal cases are excluded, the sedimentation rate was decreased significantly in 70 per cent of cases in which the rates had been elevated. In no instance did the sedimentation rate significantly increase during therapy in this group.

Those patients who died despite chemotherapeutic efforts are of special interest. In 4 fatal cases the patients failed to receive adequate treatment to qualify for the special group of 36 cases being discussed in this paper. These were either patients in the terminal stage of the disease or patients who did not tolerate significant doses of the drug. An additional 4 deaths occurred in the adequately treated group. Three of this latter group were patients who had hopelessly extensive disease involving all lobes of both lungs and whose clinical course had been rapidly progressive with evidence of tuberculous enteritis in all 3 and tuberculous laryngitis in 2. The fourth death deserves special mention because of the fact that the patient made rapid improvement with disappearance of extensive exudative lesions in the left lung. His death was sudden and unexpected, and probably was due to aspiration, through a bronchopleural fistula, of a large amount of empyema fluid from the right pleural space producing suffocation.

One patient who was receiving inadequate treatment had a small extension of the disease. At this point the dosage of promin was increased and the new lesion very promptly disappeared. One additional patient had an extension of the disease and this occurred while the patient was receiving reasonably high doses of promin. The lesion later improved but it is of interest to note that, if any inhibiting action of the drug was present, it was not adequate to prevent extension of the disease in this instance.

Brief mention should be made of our experience with some other forms of tuberculosis not included within the special group of 36 cases. In 6 cases tuberculous meningitis has been treated. Two of the patients were in early phases of the disease, but all have died. One of these lived nearly two months, suggesting that the drug may have prolonged life. No striking results have been noted in 4 cases of renal tuberculosis, but observations are incomplete. Tuberculous sinus tracts have closed in 4 instances during treatment, but not enough time has elapsed to know if they will reopen.

COMMENT

It is important to indicate some limitations of chemotherapy of tuberculosis with promin, as well as to suggest lines for further investigation. Evidence appears adequate to state that the drug, when administered as we have used it,

will not sterilize the body of tubercle bacilli and that late destructive terminal stages of tuberculosis are not influenced favorably. These late stages of tuberculosis are as different from early exudative infiltration as postpneumonic pulmonary abscess is unlike early pneumonia. In pneumococcic pneumonia and in other disease amenable to chemotherapy, early treatment is necessary to secure good results. If treatment be delayed until destruction of tissue occurs, the prompt, dramatic arrest of the infection is not to be expected. We cannot know at this time if there will be similar limitations to chemotherapy in tuberculosis but this comparison should be kept in mind.

The failure of promin to cure tuberculous meningitis brings to mind the difficulties of treatment of pneumococcic meningitis which necessitate much more intensive and more prolonged chemotherapy than is required in treatment of early pneumonia. The toxic properties of promin are too great to permit similar increase of dosage for treatment of tuberculous meningitis.

The successful treatment of experimental tuberculosis of guinea pigs with promin has been accomplished when treatment was delayed for six weeks after infection. Biopsy of lesions in the liver at this time has demonstrated that simple discrete tubercles alone were present when treatment was started (7). Caseation necrosis with tissue destruction was not observed before treatment in these experiments. Such lesions may be comparable to recent pulmonary infiltrations in man. The clinical evidence suggests possible therapeutic effect especially in those patients whose lesions are more comparable to those of guinea pigs, and in which the tolerated dose more nearly approaches that of the animals.

Further trial of promin in treatment of pulmonary tuberculosis appears justified. The results obtained in the present report suggest that emphasis should be placed on study of recent lesions without evidence of destruction of tissue or extensive fibrosis and that treatment of terminal phases of the disease should not be encouraged.

If it is possible to modify the toxic and therapeutic properties of the sulfone series of drugs as favorably as has been accomplished for the sulfonamide series, we may anticipate further progress in clinical chemotherapy of tuberculosis.

SUMMARY

A total of 106 patients have received promin for treatment of tuberculosis during the past year. Only 36 of these have received doses sufficiently large for sufficiently long periods to be included in the present study.

Improvement appeared to be most rapid and consistent in patients who had recent lesions of exudative type without extensive destruction of tissue or prominent fibrosis. Since lesions of this type tend to improve spontaneously in a large percentage of instances it could not be determined definitely whether or not the drug contributed to the rapid improvement of the present series.

Apparent reversal of sputum from positive to negative was observed in 39 per cent (14 cases) of the adequately treated group after four to twelve months of chemotherapy. Apparent closure of cavities was observed in 28 per cent (10 cases) of this group. Sedimentation rate improved to a significant degree

in 70 per cent of those cases in which the rate had been elevated before therapy. Four patients have died despite adequate therapy, 3 of these being in obvious terminal phases of the disease before treatment. In one additional case an extension of the disease developed while the patient was receiving therapy.

Six patients suffering from tuberculous meningitis have been treated for relatively brief periods but all have died. Observations are incomplete in other types of extrapulmonary tuberculosis and no conclusions are warranted at this time.

The drug must be employed with considerable caution because of its tendency to produce anaemia. Concentration of haemoglobin, erythrocyte, reticulocyte and leucocyte counts must be followed carefully to avoid excessive destruction of blood and dosage must be regulated accordingly. One case of agranulocytosis has been observed.

Further study of chemotherapy of human tuberculosis with compounds of the sulfone series appears advisable. These studies should be carried out only when facilities are adequate to observe the necessary precautions in use of these moderately toxic drugs. Large, well controlled series of cases, in which the patients have been treated with adequate doses, will be required before judgment can be passed. Emphasis should be placed on those cases in which there are recent pulmonary lesions of exudative type, without extensive destruction of tissue or fibrosis.

SUMARIO

Durante el año pasado 106 enfermos en total han recibido promina para el tratamiento de la tuberculosis, pero sólo 36 de ellos recibieron dosis suficientes durante períodos suficientemente largos para ser comprendidos en el estudio actual.

La mejoría pareció ser más rápida y constante en los enfermos que mostraban lesiones exudativas sin extensa destrucción de tejidos o fibrosis pronunciada. Como las lesiones de este género suelen mejorar espontáneamente en un elevado porcentaje de casos, no pudo determinarse definitivamente si la droga contribuyó o no a la rápida mejoría observada en la serie actual.

En 39% (14 casos) del grupo tratado adecuadamente observóse un aparente cambio del esputo de positivo a negativo al cabo de 4 a 12 meses de quimioterapia, y en 28% (10 casos) notóse cierre aparente de las cavernas. El índice de sedimentación mejoró significativamente en 70% de los casos en que había sido elevado antes de la terapéutica. Cuatro enfermos han muerto a pesar de recibir una terapéutica adecuada, pero tres de ellos se encontraban manifiestamente en las fases terminales del mal antes de ser tratados. En otro caso se manifestó una extensión de la enfermedad mientras el enfermo estaba en tratamiento.

Seis enfermos que padecían de meningitis tuberculosa han sido tratados por períodos relativamente breves, pero todos han muerto. Las observaciones son incompletas en otras formas de tuberculosis extrapulmonar y no está justificado sacar todavía deducciones.

Hay que emplear la droga con suma cautela debido a su tendencia anemizante,

observando cuidadosamente la concentración de hemoglobina y las fórmulas eritrocitaria, reticulocitaria y leucocitaria, a fin de evitar toda acción destructiva sobre la sangre y graduar la dosis debidamente. Se ha observado un caso de agranulocitosis.

Parece conveniente verificar otros estudios de la quimioterapia de la tuberculosis humana con compuestos de la serie de los sulfones, pero deben llevarse a cabo estos estudios únicamente cuando hay medios adecuados para observar las precauciones que se necesitan al emplear drogas moderadamente tóxicas como son ésas. Antes de poder dirimir el punto se necesitarán series bien controladas y numerosas de casos que reciban dosis adecuadas. Hay que hacer hincapié en los casos en que existen recientes lesiones pulmonares de forma exudativa sin extensa destrucción de los tejidos o fibrosis.

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DISCUSSION

Dr. H. S. Willis, Northville, Michigan: The vicissitudes that attend experimental work like this under discussion are many. Virulence of culture, size and manner of dose, duration of infection when the drug is applied, its manner of application, the animal strain, the health and care of the animals—these among other variations may be almost infinite and may greatly modify the outcome of the experiment. Hence the need of great caution and great wisdom in evaluating results. To make the grade, an experiment must run the gauntlet of these vicissitudes and, at the end, must stand squarely on its merits—if merits it claims.

In the paper just presented, results have been shown in the treatment of experimental tuberculosis that are as favorable as those in any series of experiments which have come to my knowledge. Guinea pigs infected with a lethal dose of tubercle bacilli have survived far beyond the period of expectancy and some of them indefinitely. This looks like a significant fact and one which justifies, even urges, continued experimentation. The results reported are intriguing and tantalizing. All of us hope to hear of further progress in this work. Drs. Woodruff and Jocz at Maybury Sanatorium have used promin in a small series of experiments with favorable results.

How difficult it is to carry experimental results over into clinical medicine! Again, pitfalls abound, especially such obvious ones as clinical evaluation, selection of cases, clinical comparison of "similar" cases under different types of treatment, determination of dose and its continuation, incidence of complications and their significance. We like our clinical results to be sharp, clear, unequivocal; we like our treatment to make the patient well. Short of this, we must be able to answer the easily made and sometimes unwarranted criticism of "how do you know" the treatment produced the results claimed.

It is with a good deal of trepidation that I enter this discussion of the clinical aspects of the work. The workers have laid a broad foundation. They have classified their cases well and have arrayed the results against a background of clinical experience. They have been careful to detect adverse effects produced by promin—especially by careful and frequent observations of the blood. Complications have been few. Several of their patients have cleared their disease at a more rapid rate than might have been expected and more rapidly than the average under ordinary, good care.

On the other hand, a good many of their cases under promin have run the "garden variety" course. The authors seem to have been wise in selecting the early, exudative case for treatment. They did this with their eyes open to the fact that, when this type of lesion does clear, it clears rather rapidly and satisfactorily, irrespective of drugs. How much significance is to be attached to the incidence of rapid clearing among their cases I do not know, for clinical experience teaches me that tuberculosis is tricky and often unpredictable. I'm afraid I must remain skeptical yet on this point. One can agree with them that a drug is not likely to produce absorption of fibrous or scar tissue or to resuscitate the terminal case.

Closure of cavities is mentioned. The closure of cavity is essentially a mechanical issue. It is difficult to see how a drug could exert influence in this way.

At Maybury Sanatorium Dr. Samuel Spencer has used promin clinically over a period of several months. He gave the drug to patients with pulmonary tuberculosis—most of them far advanced—and to several with tuberculous empyema. As a rule he administered it by mouth. In the empyema cases it was injected into the pleural space. Doses ranged from 1.2 to 2.0 g. per day. Blood levels were determined at monthly intervals. Daily administration of 1.2 to 2.0 g. resulted in levels ranging from 0.5 to 1.7 mm. per cent.

The results in the 23 cases were discouraging, in the main. In 9 cases discontinuation was necessary within a few days of its beginning because of anorexia, nausea, vomiting or drop in haemoglobin. It is interesting to observe in this connection that the administration of gelatin with promin led to great diminution of nausea and vomiting. This procedure was suggested by Dr. E. A. Sharp of Parke, Davis & Co. One patient developed peripheral neuritis from which he later recovered. Three patients showed clinical and roentgenological improvement beyond the expected, and this was attributed to promin. It should be pointed out, however, that all 23 cases were in what one might call an unfavorable group and, as such, cannot be compared with the type of case just reported upon, namely, the exudative type. Looked at from the most uncritical way, our experience has been unpromising.

I think one can endorse the whole effort of the essayists enthusiastically. We can be genuinely glad over the progress reported on the experimental part of the work, intelligently interested and at the same time skeptical of clinical results to date. I would endorse the effort and ask for continuation. I believe promin is not the answer. Who knows, however, what some of the siblings of promin might do. It is encouraging to know that the manufacturers are busily at work on several of promin's cousins and that several clinicians and pathologists are prepared to apply them.

PLEURAL EFFUSIONS IN PULMONARY TUBERCULOSIS[1, 2, 3]

A Clinicopathological Study

BURGESS GORDON, ROBERT CHARR AND J. WOODROW SAVACOOL

Pleural effusions have been investigated with special reference to their pathogenesis and the mechanical factors favoring progression. The important relationship to parenchymal disease of the lung has been noted. Pathological and clinical data are correlated with the view of suggesting criteria for prognosis and a plan of treatment.

The material was derived from 80 selected cases at the Chest Department of the Jefferson Hospital and the White Haven Sanatorium; 35 were studied at autopsy. The lungs studied postmortem were injected with a radiopaque substance and X-ray films were used for determining the location and characteristics of the blood vessels. The usual bacteriological and histological methods were employed.

The effusions are divided into two general groups, purulent and nonpurulent. In the former are included the serous, serofibrinous and haemorrhagic, and in the latter, tuberculous empyema with or without superimposed pyogenic infection. While the incidence of spontaneous effusion is rare as compared with the occurrence in artificial pneumothorax, the pathogenesis, prognosis and the treatment are fundamentally the same. Therefore, the observations in both groups are discussed together. Effusions resulting from injury of the chest wall and nontuberculous empyema are not discussed in the present study.

The pathological findings are as follows: In 20 of the necropsied cases, the fluid was nonpurulent, that is, serous, serofibrinous or haemorrhagic. But, in all, tubercle bacilli were found either in the cultures or in the sediment examined microscopically. The normal lustre of the pleura was lost, the surface being covered with fibrinous exudate. Superficial tubercles were common, especially in the anterior surface of the lung; the posterior surface showed marked congestion, but definitely fewer caseous nodules. On section, large caseous bodies were found along the anterior portions and the sternal borders of the upper lobes. The pulmonary parenchyma between the nodules showed remarkable congestion; likewise the pleura which covered these congested lesions showed increased vascularity. Numerous subpleural tubercles of varying sizes were easily seen. In the histological examinations tubercles were discovered not only in the subpleural zones, but in the pleura itself, indicating that the tubercle bacilli in the fluid probably came from the subpleural lesions. According to the clinical history, the effusion at the onset usually had been clear, that is, not turbid, and

[1] From the Department for Diseases of the Chest, Jefferson Hospital, Philadelphia, and the White Haven Sanatorium, White Haven, Pennsylvania.

[2] A part of the expense for this investigation was defrayed from a grant given in memory of Howard A. Davis.

[3] Read before the meeting of the Association of American Physicians, Atlantic City, May 5, 1942.

tubercle bacilli were discovered with great difficulty; in some cases a positive culture had not been obtained. But as time passed, the fluid gradually became turbid, although the rate of its accumulation became slow. Eventually positive cultures were obtained and bacilli were found in the sediment.

In haemorrhagic effusions there was acute congestion of the pleura with engorgement of the subpleural pulmonary parenchyma adjacent to the tubercles; also vascular dilatations were noted in the roentgenograms of the lungs injected with radiopaque substance. Evidently these vascular changes occurred before caseation actually set in, suggesting that spontaneous haemorrhagic effusion probably is a precursor of caseation. It appeared that haemorrhagic effusion gradually became nonhaemorrhagic as the pleura thickened and as subpleural congestion disappeared.

In the areas of caseation the blood vessels were narrow and many of the small branches and the capillaries disappeared altogether, some of the arterioles showing definite thrombi. With caseation the blood vessels were squeezed flat and held empty. Absolute ischaemia existed within the nodules. Ultimately, to a certain extent, as the direct result of ischaemia, the caseous nodules liquefied, forming cavities.

In 4 cases the caseous nodules situated near the anterior surface of the lung perforated through the pleura, apparently through the centre of the tubercles. The pleura covering the nodules was thin and semitransparent and free from adhesions. In following these perforations deeper into the pulmonary parenchyma it was found that the tracts led into irregularly shaped small, acute cavities. These changes were most common anteriorly due perhaps to the ballooning-out effect of the anterior portion of the lung during respiration. Contributing to this mechanism is the attachment of the ribs to the rigid spinal column posteriorly and to the more flexible sternum anteriorly, which allows greater expansion of the lung in the front part of the chest. Also, when the patient lies on his back, the common practice, the above factors become more influential. In one case a tear of the pleural adhesion between the mediastinum and the apical emphysematous blebs surrounding fibrotic tuberculous nodules was the cause of a small amount of serosanguineous effusion. The blood probably originated in the rupture of terminal bronchial arteries rather than the pulmonary vessels, since it is the bronchial artery which supplies capillaries to the pleura. Actual tear of the adhesions between the parietal and visceral layers of the pleura was found in 8 cases of chronic fibro-ulcerative tuberculosis with considerable pleural thickening; in each instance the tear was located along the axillary aspect of the lung.

Fibrosis of the pleura apparently originated in the parenchymal surface of the visceral pleura; projections of newly formed fibrous tissue extending into the lung was noted. In the absence of acute exacerbation, the thickened pleura was unusually devoid of blood vessels, but in cases with acute relapse or spontaneous pneumothorax many blood vessels were seen within the thickened pleura. This suggested that occasional small recurrences of effusion in certain patients were due to the disturbances of the vessels.

The outstanding effect of a long-continued effusion on the pulmonary parenchyma was that of diffuse fibrosis. Pulmonary blood vessels were markedly sclerosed resulting in generalized ischaemia of the lung. The proliferation of fibrous tissue was most marked in the peripheral areas of the lung; in some cases there was deep penetration into the lung. It was interesting that despite the fibrosis, caseation continued. This raised a pertinent question as to the practice of allowing pleural fluids to remain for long periods of time as a means of treating the diseased lung. Apart from the fact that pleural fluid may accomplish very little in the way of healing, there is the possibility of permanent atelectasis with resulting bronchiectasis, abscess, displacement phenomena and other complications.

Summarizing the pathological findings, which in a measure explain the clinical manifestations, it is evident that the greatest number of cases of pleural effusion complicating pulmonary tuberculosis were directly associated with extension of subpleural tuberculous lesions, and that the formation of the fluid was the precursor of serious complications, even though the amount of fluid may have been insignificant. The more acute the tuberculous process, the more frequently was the effusion a complication. The more chronic and proliferative were the tuberculous lesions, less often and less serious was the occurrence of fluid. It is interesting that there was no instance of pleural fluid in the cases of pneumonoconiosis with complicating tuberculosis, a possible explanation being the tendency of the pulmonary fibrosis to hold the tuberculous process in abeyance. The age of the patients had no definite bearing as shown by 4 patients in the sixth and seventh decades with acute tuberculous pneumonia. On the other hand, much younger patients with more chronic and fibrotic lesions seldom developed fluid, and when they did, the fluid was nonpurulent though tuberculous.

Utilizing the pathological material and clinical observations in the management of serous, serofibrinous and haemorrhagic effusions the main routine has been repeated aspirations; the pleural cavity was kept as free of fluid as possible. Rendering the pleural surface free from contact with fluid prevented the pleura from becoming oedematous and covered with thick layers of fibrin which would harbor the tubercle bacilli for potential reinfection. The favorable results suggest that a state of pleural fibrosis progressing favorably will succeed in covering the superficial tubercles, the aetiologic foci of the effusion. In certain cases, before repeated aspirations were instituted, thoracoplasty seemed advisable in order to bring the pleural surfaces into apposition and thus avoid the danger of rupture of tubercles with the subsequent development of empyema. Repeated aspirations resulted in a reduction in the formation of fluid, lowered bacillary count and decreased toxaemia. And in a few instances, as noted also by Rosenblatt (1) it was possible to convert the pleural effusion into an artificial pneumothorax with a satisfactory influence upon the lung. In guarding against pulmonary trauma and perforation of the pleura all patients showing large subpleural tubercles on thoracoscopic examination were advised against loud talking, laughing, sneezing or coughing, since such acts will increase the intrapulmonary

pressure and thereby rupture the caseous subpleural tubercles, especially in associated pneumothorax where the supporting effect of the chest wall is lost.

It has been stated that frequent thoracocentesis causes sinus formation. On the contrary, infrequent aspiration, which allows a steady rise of the intrapleural pressure due to the accumulation of the pleural fluid, and tilting of the aspiration needle are the important contributing causes. The needle should always be introduced directly through the chest wall; tilting the needle will widen the tract and favor sinus formation. In chronic effusion with pleural fibrosis the peripheral portion of the diaphragm may become adherent to the chest wall with complete obliteration of the costophrenic sulcus. As the pleural fibrosis continues the outer fringe of the diaphragm gradually is drawn upward. When this occurs a pocket is formed between the medial surface of the diaphragm and the lung in which the fluid collects. In removing the fluid, an 18 gauge curved needle is useful since it may be directed easily into the pocket by riding over the peaked diaphragm. Following each aspiration, the patient should lie on the opposite side for one or two hours, thereby permitting the needle tract to close. Whenever possible aspiration of the fluid as well as the administration of the initial pneumothorax should be done in the posterior axillary line in order to avoid puncturing the superficial caseous nodules which, according to the pathological studies, are more numerous in the anterior part of the lung. Furthermore the patients experience less pain when a needle is introduced in the posterior axillary than in the anterior axillary region. With marked fibrinous exudate, sterile physiological salt solution has been useful to thin out the fluid, thereby facilitating aspiration. Antiseptic solutions were effective and in some cases seemed to coagulate the fibrinous exudate, especially in haemorrhagic fluids, thus favoring the inclusion of tubercle bacilli in the meshes of the fibrin. In the patients with small residual pleural cavities irrigation of the cavity with physiological salt solution followed by the instillation of a sclerosing agent, quinine urea hydrochloride, 5 to 10 per cent, 1 to 10 cc., aids in developing fibrosis of the pleura and eventual closure of the space. This technique has also been effective in closing sinuses caused by aspiration. Pledgets soaked in quinine urea hydrochloride, 5 per cent solution, are introduced into the sinus every two days and allowed to remain for about fifteen minutes. After a week or two, the sinus is usually closed.

Spontaneous haemorrhagic effusions were also treated by repeated aspiration. When pyogenic organisms are discovered in the fluid, sulfadiazine is administered with apparently beneficial effects. George Willauer (2) found that the drug, when given orally immediately after pneumonolysis, prevented or checked the development of pyogenic infection of the pleural fluid. The initial dose was 2 g. repeated in four hours; following the second dose 1 g. was given every four hours for three days. It was noted in some cases that the sulfadiazine level in the pleural fluid was higher than that of the blood, the figures being 4.2 mg. for 100 cc. of blood and 5.1 mg. for the same amount of pleural fluid, indicating that the drug was retained in the pleural cavity. In persistent cases of purulent effu-

sions, with an open tuberculous cavity within the lung, thoracoplasty has been the procedure of choice; in frank empyema, due chiefly to superimposed pyogenic infection, open drainage and irrigation were used in preparation for thoracoplasty.

CONCLUSIONS

1. The chief factor in the development of pleural fluid is the direct relation of tubercles in the lung to the visceral pleura. Tuberculous empyema results when a caseous nodule ruptures into the pleural cavity.
2. The tubercles located in the anterior part of the lung show a definite tendency to rupture probably due to the greater thoracic movements in the anterior chest.
3. Effusions occur more commonly in acute tuberculosis regardless of the age of the patient; in fibroid tuberculosis effusions are comparatively rare even in young patients.
4. Vascular changes in the pleura and subpleural tissues, notably increased vascularization, are significant in the pathogenesis of pleural effusion, especially the haemorrhagic form.
5. The outstanding effect of pleural effusion upon the lung is diffuse fibrosis of the pulmonary parenchyma without necessarily arresting the process of caseation.
6. In serous, serofibrinous, haemorrhagic effusions and in certain cases of pure tuberculous empyema with the pulmonary lesions controlled, repeated aspirations brought about satisfactory results.
7. Sulfadiazine has been of value in controlling superimposed pyogenic infection of the fluid. Quinine urea hydrochloride used as a sclerosing agent aids in obliterating residual pleura spaces and pleurocutaneous sinuses.

CONCLUSIONES

1. El principal factor en la producción de derrame pleural consiste en la relación directa de los tubérculos pulmonares con la pleura visceral. Sobreviene un empiema tuberculoso cuando un nódulo caseoso se abre en la cavidad pleural.
2. Los tubérculos localizados en la parte anterior del pulmón revelan una tendencia bien definida a la rotura, probablemente debido a la mayor amplitud de los movimientos torácicos en la porción anterior del pecho.
3. Los derrames son más frecuentes en la tuberculosis aguda, independiente de la edad del enfermo; en la forma fibroidea son comparativamente raras aun en los jóvenes.
4. Las alteraciones vasculares en la pleura y tejidos subpleurales, y en particular la hipervascularización, revisten importancia en la patogenia del derrame pleural y en particular en la forma hemorrágica.
5. El efecto más notable del derrame pleural sobre el pulmón consiste en una fibrosis difusa del parénquima pulmonar sin interrupción forzosa del proceso de caseación.
6. En los derrames hemorrágicos serosos, serofibrinosos y en ciertos casos de

empiema tuberculoso y ya cohibidas las lesiones pulmonares, las aspiraciones repetidas dieron resultado satisfactorio.

7. La sulfadiazina ha resultado de valor para cohibir la infección piógena sobrepuesta del líquido. El clorhidrato de quinina y urea utilizado como esclerosante ayuda a obliterar los espacios pleurales residuales y las fístulas pleurocutáneas.

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TUBERCULIN REACTION IN OLD AGE

PETER AMAZON[1]

The development of satisfactory techniques for the detection of cases of tuberculosis in the general population has not yet been attained. Proper methods of case-finding are fundamental in both the prevention and treatment of tuberculosis.

If the chest X-ray film is selected as the standard case-finding procedure for the detection of pulmonary tuberculosis, it might be pointed out that the heart and bony structures of the thorax frequently conceal significant tuberculous foci and that a diagnosis cannot always be made from a single film. Nevertheless, an X-ray film of the chest has more weight in establishing a diagnosis of pulmonary tuberculosis than any other factor.

The tuberculin reaction, however, is of minor or secondary importance in any case-finding program. The intracutaneous test with Old Tuberculin or Purified Protein Derivative tuberculin is presumed to be an index of tuberculous infection in any age group or in any community. It is employed as a method of reducing X-ray costs in survey work on the premise that it will eliminate those persons who have never been infected. This assumption has been amply disproved by the recent use of chest X-ray films and tuberculin tests in the same group. The results show that there is radiographic evidence of tuberculous infection in a considerable proportion of those who do not have a positive tuberculin test. This surprisingly high percentage of healed primary tuberculosis in people who do not react to tuberculin definitely limits the use and the efficiency of this test in case-finding.

The frequency of X-ray evidence of tuberculous infection in the presence of negative tuberculin reactions is variously reported from 13 to 50 per cent (table 1). The high incidence of calcification among tuberculin-negative persons implies that the tuberculin test is not specific for these lesions; or that the degree of tuberculization is not sufficient to be detected by the tuberculin test. But, I believe, there is no reason to doubt the tuberculous aetiology of these calcifications.

Many explanations, such as obsolete infections and absence of continued reinfections, have been submitted as reasons for this lack of allergy. But whatever the explanation may be, this high incidence of radiographically demonstrable calcification among tuberculin-negative persons definitely limits the application of the tuberculin test in epidemiological studies of tuberculous infection. The tuberculin test can no longer be used as a screen to reduce X-ray costs in survey work.

It is important to distinguish between the application of the tuberculin test in epidemiological surveys for the establishment of infection rates for comparison at different times and different communities and the clinical use of the tuberculin reaction for case-finding and diagnostic work. In this field, the tuberculin

[1] 918 Saint Marks Ave., Brooklyn, New York.

reaction is invaluable for the identification of doubtful or incipient disease but not infallible.

TABLE 1

Incidence of calcifications in tuberculin-positive and tuberculin-negative groups

AUTHOR	AGE	TUBERCULIN	CALCIFICATIONS IN TUBERCULIN-POSITIVE REACTORS	CALCIFICATIONS IN TUBERCULIN-NEGATIVE REACTORS
			per cent	*per cent*
Crimm *et al.* (1)	2 to 19 years	OT & PPD	59	23
Nelson *et al.* (2)	Infants & Children	OT & PPD	42.5	43
McKneely (3)	School Children	PPD	20	13
Gass *et al.* (4)	School Children	OT	50	50
Lumsden *et al.* (5)	School Children	PPD	46.5	42.7
Dearing (6)	Children & Adults	PPD	35.4	34.2
Alt *et al.* (7)	College Students	PPD	71.3	28.7
Olson *et al.* (8)	Infancy to 55 years	PPD	70	44

PROCEDURE

The scope of the present study is confined to the tuberculin reaction in old age and the X-ray study of both the negative reactors and positive reactors.

Old Tuberculin was used by the Mantoux test. The initial dose was 0.1 mg. and the negative reactors were retested with 1 mg. Reactions with areas of induration of 5 mm. or more in diameter were recorded as positive. Reactions with erythema but without induration and those with areas of induration of less than 5 mm. were recorded as negative. The readings of the degrees of reaction were as follows: areas of induration of 5 to 10 mm. in diameter were read as 1 plus, those of 10 to 20 mm. as 2 plus, those exceeding 20 mm. as 3 plus, and those with both induration and necrosis as 4 plus. Reactions were read forty-eight hours after the injections.

All inmates of the Brooklyn Hebrew Home and Hospital for the Aged, 619, were examined. There were 241 men and 378 women: 112 were in the age group of sixty-five to sixty-nine, 156 were in the age group of seventy to seventy-four, 152 were in the age group of seventy-five to seventy-nine and 199 were over eighty years of age; 97 per cent were foreign-born, 75 per cent were born in Russia and about 50 per cent arrived in this country since the first World War.

In Europe they had lived in industrial centers and large cities. Nearly all settled in large cities in this country and secured employment in light manufacturing, such as wearing apparel. During the past three centuries, the Jews have lived in towns or cities in preference to farms or rural areas. In such a group, one would expect to find a high incidence of healed or obsolete pulmonary tuberculosis.

RESULTS

Tuberculin reaction to 0.1 mg. Old Tuberculin: In the age group sixty-five to sixty-nine, 10 per cent failed to react to tuberculin whereas in the age group over eighty, 26 per cent had a negative tuberculin reaction. For the entire group of 619 individuals over sixty-five years of age, 137, or 22 per cent showed no reaction to 0.1 mg. of Old Tuberculin. These findings are identical with

those of Dearing who found 21 per cent negative reactors among 111 individuals over sixty years of age of native American stock in Giles County, Tennessee.

X-Ray study of negative reactors: This group of negative reactors was studied from a radiographic standpoint to determine the incidence of healed primary tuberculosis and reinfection tuberculosis. A person was classified as positive only when the character of the lesion was definite. Doubtful cases were considered negative. The following types of lesions were considered as tuberculous in origin. Any calcification in either the parenchyma or tracheobronchial nodes was considered as suggestive of a healed primary focus. Apical pleurisy was not considered tuberculous in origin unless associated with definite infiltration which projected into the lung parenchyma. Apical and infraclavicular infiltrations having the appearance of tuberculosis were classified as suggestive of reinfection tuberculosis. Due consideration must be given to confusing roentgenological shadows in the age group under consideration. They are irregular calcifications of the costal cartilages, cross sections of vessels and bronchi. X-ray study of 133 negative reactors to 0.1 mg. Old Tuberculin revealed that 48,

TABLE 2

TUBERCULIN REACTION TO 0.1 MG. OLD TUBERCULIN			X-RAY FINDINGS							
			Negative		Healed primary tuberculosis		Reinfection tuberculosis		Total tuberculous infection	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Negative reactors	133	38.5	85	64	36	27	12	9	48	36
Positive reactors	212	61.5	133	62	51	24	28	13	79	37
Total tested	345	100	210	61	93	27	42	12	135	39

or 36 per cent, (table 2) showed evidence of tuberculous infection. The incidence of healed primary tuberculosis was 36, or 27 per cent, whereas the incidence of reinfection tuberculosis was 12, or 9 per cent. This is a surprisingly high percentage of tuberculous lesions which would have been missed if the only criterion had been the tuberculin test.

Interpretation of films by other observers: This high incidence of 36 per cent (table 2) of radiographically demonstrable tuberculosis among tuberculin-negative reactors is not in harmony with the generally accepted views of tuberculin allergy in relation to evidence of tuberculous infection. Accordingly, these 133 films were submitted to seven competent specialists. These observers were requested to read the films with particular reference to the presence or absence of evidence of tuberculosis, either primary or reinfection. At the time the films were read, these observers had no knowledge of the results of the tuberculin test. A summary of their findings is recorded in table 3. According to their interpretations, the total incidence of tuberculous infection varied from 26 per cent to 62 per cent. The average was 47 per cent. This would appear

to confirm the observations that evidence of tuberculous infection is present in a considerable proportion of the aged who do not have a positive tuberculin reaction. If this is true, and it has been confirmed by other investigators in different age groups, the level of tuberculous infection is appreciably higher than is shown by the use of the tuberculin test alone.

Tuberculin reaction to 1.0 mg. Old Tuberculin: Of the original 133 negative reactors to 0.1 mg. of Old Tuberculin, 120 were retested with 1.0 mg. It is significant that 77 per cent of this group remained inert to the second dose.

X-ray study of positive reactors: There were 212 reactors to 0.1 mg. of Old Tuberculin. This included 84 with a 1 plus reaction, 74 with a 2 plus reaction, 36 with a 3 plus reaction and 18 with a 4 plus reaction. X-ray study of this group of reactors revealed that 79, or 37 per cent, showed evidence of tuberculous lesions.

Judged by the same standards, the incidence of tuberculosis is about the same in the tuberculin-positive group as in the tuberculin-negative group.

TABLE 3

NAME	TOTAL	NEGATIVE		HEALED PRIMARY TUBERCULOSIS		REINFECTION TUBERCULOSIS		TOTAL TUBERCULOUS INFECTION	
		Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Rob	133	99	74	29	22	5	3.7	34	26
Rei	133	90	68	27	20	16	12	43	32
Ama	133	85	64	36	27	12	9	48	36
Ehr	133	65	49	49	37	19	14	68	51
Lev	133	61	46	49	37	23	17	72	54
Bri	133	58	44	40	30	35	26	75	56
Rog	133	51	38	59	44	23	17	82	62
Lou	133	50	38	69	52	14	10	83	62

This study has brought to light some cases of reinfection tuberculosis in the aged with a negative tuberculin reaction. Further studies of this group are in progress and will be reported later.

CONCLUSION

In this group of aged city-dwellers, radiographic evidence of pulmonary tuberculosis has been demonstrated to exist in a surprisingly high percentage of those who do not react to the intracutaneous tuberculin test. It must therefore be concluded that a negative tuberculin reaction does not exclude tuberculous infection and that the tuberculin test cannot be employed as a method of reducing X-ray costs in survey work.

SUMMARY

References are quoted to illustrate the findings of other investigators of a high percentage of roentgenologically demonstrable tuberculous infection in tuberculin-negative individuals.

A study of 619 persons over sixty-five years of age with tuberculin tests and X-ray films is reported; 22 per cent did not react to 0.1 mg. Old Tuberculin; 77 per cent of these were inert to 1.0 mg. Old Tuberculin; 37 per cent of the reactors to Old Tuberculin showed X-ray evidence of tuberculous infection whereas 36 per cent of the nonreactors to Old Tuberculin showed roentgenological evidence of tuberculous infection.

SUMARIO

Preséntanse datos bibliográficos para ilustrar los hallazgos de otros investigadores que han observado un elevado porcentaje de infección tuberculosa roentgenológica demostrable en individuos negativos a la tuberculina.

Preséntase un estudio de 619 personas de más de 65 años de edad en que se hicieron reacciones a la tuberculina y se obtuvieron roentgenografías: 22% no reaccionaron a 0.1 mg de tuberculina vieja; 77% resultaron inertes a 1 mg; 37% de los reactores revelaron signos roentgenológicos de infección tuberculosa comparado con 36% entre los inertes.

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ULCERATIVE TUBERCULOSIS OF THE STOMACH[1, 2]

PHILIP H. HARTZ AND ARY VAN DER SAR

Though enormous numbers of tubercle bacilli pass through the stomach in advanced pulmonary tuberculosis, gastric tuberculosis is exceptional. In a study of the gastrointestinal findings in 1,000 autopsies performed in the City of Chicago Municipal Tuberculosis Sanitarium and of 1,000 clinical cases referred to the gastrointestinal department of this Sanitarium (of which latter group 102 cases came to autopsy) Hardt and Cohen (1) found only one case: a perforation of a tuberculous lymph node into the stomach. Broders (2), reporting the first case of the Mayo Clinic, estimated that prior to 1917 only 49 undubitable cases of gastric tuberculosis had been published and Eusterman and Balfour (3) found only 9 additional unmistakable cases since Broders' report. Other figures can be found in the paper of Popoff (4). He cites Crawford and Sawyer, who did not once find gastric tuberculosis in 1,400 autopsies on tuberculous subjects and also an analysis by Chaffin of 211 cases of gastric tuberculosis reported to the end of 1937, of which only 51 are considered as unquestionable. Not included in these figures is the occasional finding of a few tubercles in miliary tuberculosis, which is not uncommon (Kaufmann (5)) and of which we too saw several cases.

CASE REPORT

A colored man, fifty-nine years old, entered the hospital with a history of coughing, hoarseness and loss of weight. He sweated much and tired easily. Anorexia was present and sometimes the patient vomited after a fit of coughing. Diarrhoea was not frequent. The wife of the patient had died ten years ago of asthma (?). On admission the patient appeared very ill and emaciated. The pulse was feeble and rapid. The heart beat was seen and felt in the medio-clavicular line in the fifth intercostal space; the cardiac dulness was enlarged to the left. There was a systolic murmur at the apex. The inferior margins of the lungs were immobile and showed a downward displacement. The percussion sound was dull; everywhere bronchitic râles were heard and, especially on the left side, bronchial breathing and crepitating râles. In the sputum many acid-fast bacilli were found. The liver and spleen could not be palpated. Examination of the urine showed the specific gravity to be 1016; albumen and urobilin positive; no glucose; in the sediment were many leucocytes. The presence of tubercle bacilli in the urine was proved by culture (Dr. A. W. Pot). The X-ray pictures of the lungs showed many well delimitated probably bronchogenic lesions. The condition of the patient deteriorated rapidly and death followed after eleven days.

[1] From the Public Health Service, Curacao, N. W. I.

[2] Read at the Jornádas Tisiológicas Nacionales at San Cristobal, Venezuela, March 21, 1940.

AUTOPSY

Autopsy was performed fifty minutes after death. In both lungs many caseous nodules, some well encapsulated, were found. There was extensive tuberculous bronchitis, peribronchitis and bronchiolitis. Intestinal tuberculosis was severe, the mesenteric lymph nodes were caseated. In the kidneys a few small embolic tuberculous lesions were found.

The stomach was empty and well contracted. The mucous membrane showed distinct folds, the color was pale grayish-red. In the lesser curvature, 3 cm. distant from the cardia two ulcers were found in a more or less symmetrical position. The distance between the two ulcers was 2 cm. The ulcers measured 4 × 10 mm. and 6 × 10 mm., respectively (figure 1). The longitudinal axis of one ulcer was parallel to the curvature, that of the other more oblique. The borders of the ulcers were deeply undermined; the borders of one ulcer were connected by a narrow strip of mucosa like the handle of a basket. The bottoms of the ulcers were connected by a tract, which easily admitted a probe. The gastric wall in the cardiac region was thickened; on the external surface a few anthracotic lymph nodes, containing small areas of caseation, were seen. Incisions into the specimen, made after fixation, showed that the ulcers extended into the subserosa.

Microscopical examination: The specimen was fixed in Bouin's fluid and embedded in paraffin after treatment with methylbenzoate-celloidin. The sections were stained with haematoxylin-azophloxin, Masson's tetrachrom stain and haematoxylin-orcein. For the demonstration of tubercle bacilli, Schmorl's modification of the Ziehl-Neelsen stain (6) was used. In the neighbourhood of the ulcers the mucous membrane was oedematous, the surface epithelium high and intact between the grossly visible and microscopical ulcers. The glands were partly of the cardia type, partly corpus glands and slightly irregular in form, sometimes with cystic dilatation. In and between the cells of the surface epithelium a moderate number of lymphocytes were found and only exceptionally a polymorphonuclear leucocyte. Small numbers of these cells were seen here and there between and in the epithelial cells of the glands. Mitotic divisions were found in the necks of the glands, where they are also found in the normal stomach; they were not frequent.

The stroma of the mucosa contained a few lymphocytes and numerous plasma cells. In a few places there were small follicles, with hyaline connective tissue. Polymorphonuclear leucocytes were rare.

In the mucosa several types of lesions were found. In the first place typical small tubercles consisting of one to three giant cells, a few epithelioid cells and only little caseation (figure 2). Many of these tubercles were lying in the deeper parts of the mucosa. Often the lining cells of the glands were involved in the caseation or had disappeared to some extent, with part of the epithelioid cells lying in the glandular lumen. In other places no typical tubercles were seen. Between two glands a solitary giant cell, often closely adjacent to the glandular epithelium, was seen and several round to oval cells, two to four times the size of a plasma cell, containing 1 to 4 light staining nuclei. We believe this to be a very early stage of tubercle formation.

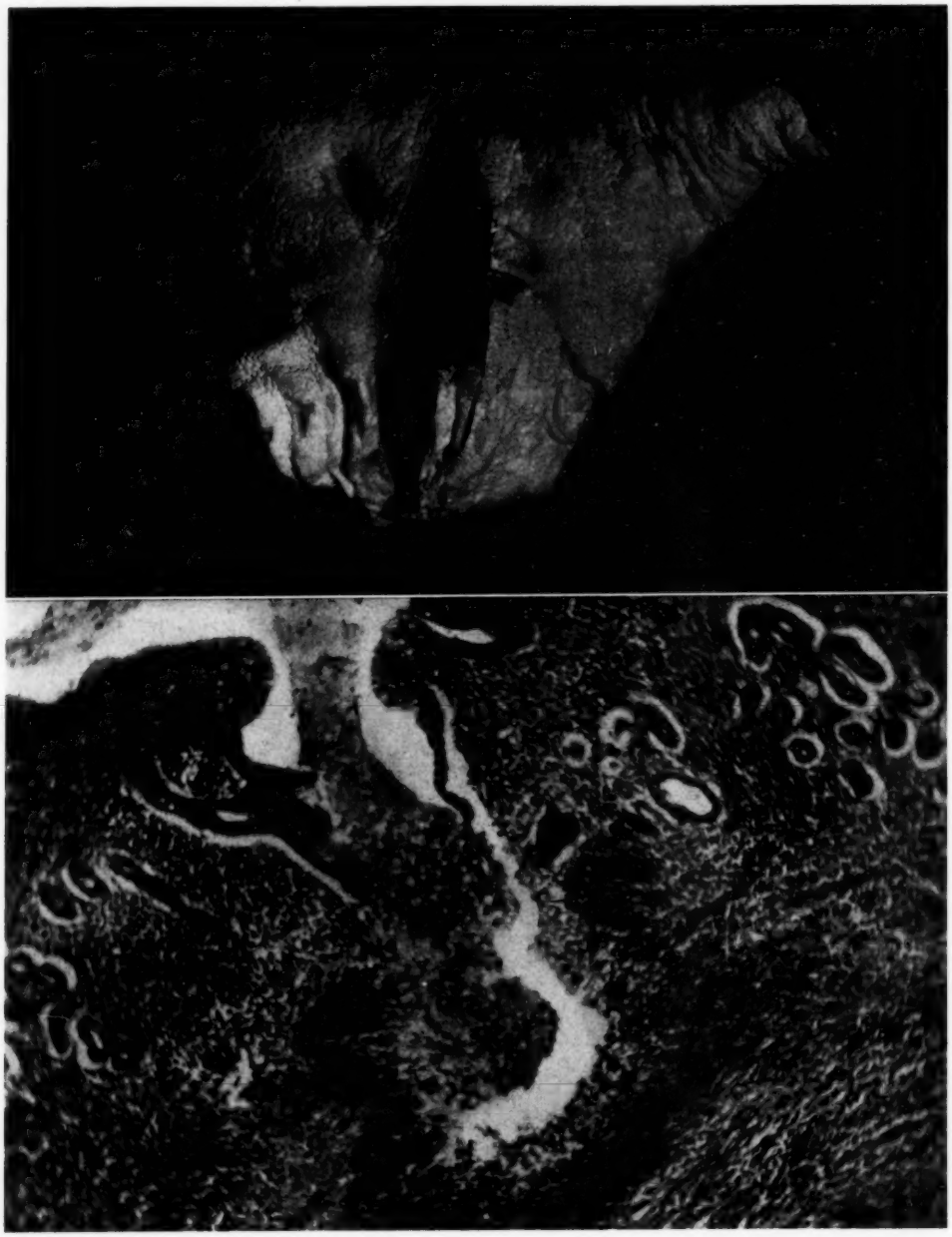

FIG. 1. (Upper) Specimen showing the cardia with the two ulcers and the distal end of the oesophagus

FIG. 2. (Lower) Small tuberculous ulcer in the mucosa. Note giant cells. 133×

By the extension of the caseation to the lumen of the stomach, microscopical ulcers were formed, which sometimes were bordered by the intact remnants of a glandular *cul de sac* and by surface epithelium, whereas at the bottom of the ulcers necrotic epithelioid cells and tuberculous granulation tissue were lying. Still another type of lesion consisted of a small abscess, occupying nearly the whole depth of the mucosa. The leucocytes in this abscess, except the most peripheral ones, were completely necrotic and did not show any nuclear staining. The abscess was surrounded by a great number of large, finely vacuolated cells, containing one or two nuclei and sometimes phagocystosed material. Between the *muscularis mucosae* and the large cells a narrow strip of tuberculous granulation tissue was found, whereas this was absent elsewhere around the abscess.

The spread of the tuberculous process by way of the lymphatics could easily be followed. In distended lymph vessels, just below the *muscularis mucosae*, sometimes degenerated leucocytes, macrophages and fibrinoid masses were seen, and in these masses giant cells of the Langhans type, epithelioid cells and a few plasma cells. In some sections the fibrinoid masses were partly covered by endothelium.

The muscular coats of the stomach were hypertrophied and the connective tissue between the muscle bundles increased and oedematous. In the muscular coats there were many areas of caseation, surrounded by tuberculous granulation tissue and also groups of smaller tubercles with little caseation.

The great ulcers showed some special features. The borders were, as mentioned before, deeply undermined and microscopical examination revealed that the undermined tissue consisted of the mucosa, the *muscularis mucosae* and a very narrow strip of submucosa. The undersurface of this tissue was partly covered by epithelium continuous with the surface epithelium. The epithelium here was not so high as the surface epithelium and many polymorphonuclear leucocytes were found in and between the cells. The ulcers reached into the thickened subserosa and showed no connection with the perigastric lymph nodes. The inner layer, adjacent to the cavity, was represented by necrotic masses, showing partly the characteristics of fibrinoid necrosis, partly of caseation. This layer varied in thickness. The necrotic masses were surrounded by granulation tissue, in some places tuberculous, in others nonspecific, with great numbers of plasma cells. Several large arteries, their lumina filled with granulation tissue, were seen entering the necrotic layer; here the vessels had become necrotic and were only recognizable by the orcein stain. In the neighbourhood of the ulcers, the muscle bundles were separated by the granulation tissue and finally destroyed. With the Ziehl-Neelsen stain many acid-fast bacilli were found in the caseous and necrotic masses, surrounding the ulcers and also in the caseous tubercles lying in the muscular coats some distance from the ulcers.

DISCUSSION

Broders (2) considers the diagnosis of gastric tuberculosis as certain only in those cases in which (*1*) the histological picture of tuberculosis is present and (*2*) the bacilli of tuberculosis are found in the depths of a typical lesion or in a lesion of indefinite histological characteristics. As these conditions were fulfilled in

our case, we believe that the diagnosis cannot be doubted. Still the possibility of a secondarily infected peptic ulcer has to be considered. The form and the location of the ulcers however make this highly improbable and to this can be added the rarity of peptic ulcers in our material (7). The location of tuberculous ulcers in the cardiac region seems to be very uncommon. Konjetzny (8) does not mention this location and Kaufmann (5) reports only one case.

No satisfactory explanation has been given for the relative immunity of the stomach to tuberculosis. In almost every case of advanced pulmonary tuberculosis the gastric acidity is diminished, a fact proved by many authors and also valid for the native population of Curacao (v.d. Sar). Superficial erosions without specific histological features are often found in the stomachs of patients dying from pulmonary tuberculosis, so that the immunity cannot be due to an intact mucous membrane. Finally, the often quoted argument of the paucity of lymph follicles in the gastric mucosa does not seem to hold true, as follicles are often found, especially in the antrum, when a large material is carefully examined.

SUMMARY

A case of ulcerative tuberculosis of the stomach is described, occurring in a colored man, fifty-nine years old, who died from pulmonary and intestinal tuberculosis. The ulcers were located in the cardiac region and were connected by a tract. Histological changes, typical for tuberculosis, were present and acid-fast bacilli could be demonstrated in the depths of the lesions.

SUMARIO

Descríbese un caso de tuberculosis ulcerada del estómago, sobrevenida en un sujeto de color de 59 años, que murió de tuberculosis pulmonar e intestinal. Las úlceras correspondían a la región cardíaca y estaban unidas por una fístula. Observáronse alteraciones histológicas típicas de tuberculosis y se encontraron bacilos ácido-resistentes en la porción más profunda de las lesiones.

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PENTOTHAL SODIUM ANAESTHESIA FOR THE TUBERCULOUS PATIENT[1]

V. R. KRUEGER

The tuberculous patient is frequently a poor risk for anaesthesia because of: (*1*) debility, (*2*) a basal metabolic rate which may be elevated, (*3*) secondary anaemia, (*4*) low vital capacity and (*5*) sputum and excessive bronchial secretion which increase the danger of postoperative atelectasis or spread of the disease. Because of the secondary anaemia and increased basal metabolic rate, it is imperative that a liberal supply of oxygen reach the blood during anaesthesia. However, because of the disease in the respiratory tract, with increased secretions and low vital capacity, it becomes difficult to get either oxygen or an anaesthetic gas absorbed. Since many of these patients require several stages of surgery, any disadvantage of anaesthesia is exaggerated by repetition.

PENTOTHAL SODIUM

A review of recent literature indicates a rather marked increase in the use of pentothal sodium for many types of surgery. However, almost all investigators (1, 2) caution against the use of pentothal sodium in the presence of respiratory obstruction or a disturbance of respiratory physiology because this agent is a respiratory depressant. No actual clinical trials in this type of patient are cited. One anaesthetist (3) using intravenous evipal in thoracic surgery noted less postoperative pulmonary complications with this agent than with nitrous oxide, tribromethanol, cyclopropane or local anaesthesia. Also shock was less severe and less frequent when evipal was used.

Pentothal sodium anaesthesia has certain special merits that make it a valuable anaesthetic agent. Among these are: (*1*) rapidity and ease of induction, (*2*) slight change in pulse and blood pressure (4), (*3*) little postoperative nausea and vomiting, (*4*) noninflammability, (*5*) minimal sweating and (*6*) few postoperative pulmonary complications. The fact that the patient does not dread repetition of the anaesthesia is a distinct advantage.

TECHNIQUE OF ADMINISTRATION

The administration of pentothal sodium at this sanatorium was initially done under the supervision of Dr. Ralph Knight, Chief of the Department of Anaesthesia, University of Minnesota. The technique used closely follows his direction. It is very similar to the technique outlined by Lundy and Adams (5).

Premedication consists of $1\frac{1}{2}$ grains pentobarbital one hour before surgery and $\frac{1}{3}$ to $\frac{1}{4}$ grain of morphine sulfate with $\frac{1}{200}$ to $\frac{1}{100}$ grain of atropine sulfate hypodermically forty-five minutes before operation.

Induction and maintenance are accomplished by intermittent intravenous injection of a 2.5 per cent solution of pentothal sodium. The patient is no longer asked to count aloud during induction since casual conversation during this

[1] From Nopeming Sanatorium, Nopeming, Minnesota.

period makes induction easier and quicker. After the patient is asleep, the face mask is applied and 100 per cent oxygen is given at the rate of 200 to 400 cc. per minute. Under deep pentothal anaesthesia, ventilation with air alone is insufficient (6) and 100 per cent oxygen used for a short period of time is not irritating. Anaesthesia is continued until the jaw is well relaxed and a rubber tracheal tube is then inserted under direct vision with a laryngoscope. The 100 per cent oxygen is continued through the tube during the entire operation. The pharynx is packed with moist gauze to prevent leakage in the event that oxygen under positive pressure should be desirable as in the case of accidental rupture of the pleura during extrapleural pneumonolysis. Intratracheal aspiration with a 16 or 18 gauge French catheter is done through the tracheal tube as often during the operation as is necessary to keep the respiratory passages clear and always at the end of the operation and before positive pressure is used.

Physiological saline or 5 per cent glucose in saline is given through the same needle that carries the pentothal. This aids in preventing shock and serves to keep the needle patent.

The character of the respirations is the principal guide as to the depth of the anaesthesia. In general it may be said that the deeper the anaesthesia, the slower and more shallow the respirations. The usual anaesthetic signs, such as size of pupils or extra-ocular movement are of little or no value when pentothal is used.

Anaesthetists familiar with thoracic surgery will recall that upon occasion, during extrapleural pneumonolysis, it may be convenient for the surgeon if respiratory movement is very slight or entirely absent. In most cases this can be anticipated and above conditions obtained by gradually increasing the frequency of the intermittent injection. Respiration is then carried out artificially by rhythmic pressure on the breathing bag so as to interfere as little as possible with the work of the surgeon. When the surgeon strips the tissues from the mediastinal structures during this operation, there may be sudden tachycardia or cough in spite of anaesthesia of sufficient depth for most surgical procedures. Anaesthesia can be temporarily increased to complete intercostal paralysis to obviate this cough reflex during an especially difficult period.

CLINICAL MATERIAL

The cases studied have been divided into two groups and include a total of 103 cases. Group I includes the last 50 cases of thoracic surgery in which local anaesthesia (metycaine 0.5 per cent) was used. Group II includes the cases in which pentothal sodium has been used to date. The pulmonary diagnoses, following the Diagnostic Standards' classification, in Group I, or those done under local anaesthesia are: 4 with moderately advanced tuberculosis and 46 with far advanced tuberculosis. The diagnoses of those done under pentothal are: 2 with clear or negative chest, 3 with minimal tuberculosis, 8 with moderately advanced tuberculosis and 40 with far advanced tuberculosis, 3 of whom also had empyema.

The surgical procedures are shown in table 1.

RESULTS

The age of the patients operated under local anaesthesia ranged from twenty to sixty-two years with an average of 39.4 years and, of this group, 41 cases were male patients and 9 were female patients. Cases with pentothal anaesthesia

TABLE 1

PROCEDURE	GROUP I (LOCAL)	GROUP II (PENTOTHAL)
Extrapleural pneumonolysis	2	14
First-stage posterior thoracoplasty	17	4
Second-stage posterior thoracoplasty	13	8
Third-stage posterior thoracoplasty	7	0
Anterolateral thoracoplasty	11	8
Revision thoracoplasty	0	2
Spinal fusion	0	4
Appendectomy	0	5
Miscellaneous	0	8
Total	50	53

TABLE 2

AVERAGE		GROUP I (LOCAL)	GROUP II (PENTOTHAL)
Age	Average	39.4 yr.	39.0 yr.
	Range of variation	20–62 yr.	20–64 yr.
Weight	Average	66.6 kilo.	62.9 kilo.
	Range of variation	44.1–84.1 kilo.	41.8–95.4 kilo.
Dose	Average	475.0 cc.	33.45 mg./kilo.
	Range of variation	300–850 cc.	18.3–65.0 mg./kilo
Duration	Average	82 min.	97 min.
	Range of variation	48–145 min.	45–180 min.
Change in pulse	Operation	+26.8 beats/min.	+20.1 beats/min.
	Postoperative	+21.2 beats/min.	+10.7 beats/min.
Change in systolic blood pressure	Operation	−20.2 mm. Hg.	−15.7 mm. Hg.
	Postoperative	−23.4 mm. Hg.	−19.3 mm. Hg.
Nausea		70%	60.3%
Emesis		70%	58.4%
Catheterization		22%	26%
Doses of narcotic postoperatively		10.5 in 4 days	10 in 4 days

ranged from twenty to sixty-four years of age with an average age of thirty-nine years.

In the latter group there were 33 male patients and 20 female patients. The remaining data are shown in table 2.

Several points of table 2 require further explanation. The change in pulse and blood pressure of the two groups can be fairly well compared in the table. When these changes are more carefully studied, the findings are even more favorable for pentothal. For example, in no case did the blood pressure fall below a pressure of 90 mm. mercury during surgery under pentothal anaesthesia and in only one case was it felt that the patient's condition approached shock during surgery. Of those patients operated under local anaesthesia, 11 cases developed blood pressure of 90 mm. of mercury or less, of which 5 were in moderately severe shock.

A closer review of the question of postoperative emesis reveals that the findings again are in favor of pentothal sodium. Of the series done under pentothal, there were 31 cases who had emesis. Of these 31 cases, 14 vomited once, 7 vomited twice and only 11 vomited three or more times. Contrast this with the 35 patients who had emesis postoperatively when surgery was done under local anaesthesia. Of these 35 cases, 3 vomited once, 7 vomited twice and 25 vomited three or more times. Postoperative emesis is both less frequent and less persistent after pentothal anesthesia.

The average dose of pentothal sodium necessary for an operation was 33.45 mg. per kilo. This average has since been considerably decreased as the experience with the drug increased. Thus, in the first 27 cases done under pentothal sodium, the average dose was 37.27 mg. per kilo. and these cases awoke postoperatively in an average of one hundred nineteen minutes. In the next 26 cases under pentothal, the average dose was 29.49 mg. per kilo. and the awakening time was fifty-five minutes. Further, 10 of the 14 cases requiring catheterization occurred in the first 27 cases. In general it may be said that a small dose of pentothal permits wakening sooner (8) and decreases postoperative complications.

Postoperative pulmonary complications were minimal in both groups I and II. In one case under pentothal sodium there was an exacerbation of a tuberculous process present in the base of the lung on the operated side. There were no cases of spread of the disease or atelectasis postoperatively.

There was one death in the series done under local anaesthesia. This patient died in shock the day following surgery. There were 4 postoperative deaths in the series done with pentothal sodium. None of these deaths were related to the anaesthesia. One occurred three days after surgery for perforated appendix with peritonitis; one, a week after surgery for carcinoma of the sigmoid with metastases; and 2 of cardiorespiratory insufficiency, forty-five days and twenty-two days after surgery, respectively.

SUMMARY

Contrary to previous reports, pentothal sodium is a safe anaesthetic for the tuberculous patient and may indeed prove to be the anaesthetic of choice for this type of patient. In general, induction is easy and pleasant for the patient, the anaesthesia is ideal for the surgeon, physiological disturbance of the cardiovascular and respiratory systems is small and the postoperative course is relatively smooth and untroubled.

SUMARIO

En contraposición a ciertos informes anteriores, el pentotal sódico constituye un anestésico inocuo para el tuberculoso y puede ser hasta el de elección para esa clase de enfermos. En general la inducción de la anestesia resulta fácil y agradable para el enfermo, la anestesia es ideal para el cirujano, pocos son los trastornos fisiológicos que provoca en los aparatos cardiovascular y respiratorio y la evolución postoperatoria es relativamente sencilla y sin perturbaciones.

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OXYGEN THERAPY IN CHRONIC SUPPURATION OF THE LUNG[1,2]

A Report of Eight Cases

ARTELL E. JOHNSON AND ANDRE COURNAND

In an attempt to determine whether the maintenance of high oxygen tension in the circulating blood might be beneficial in severe cases of chronic pulmonary suppuration, high oxygen concentrations were administered to 8 patients for periods ranging from seven to sixty-nine days. These patients had in all instances a large amount of foul expectoration and a spreading pneumonitis. Bacteriological studies indicated that the suppurations were due to anaerobic organisms.

PROCEDURE

The oxygen was routinely administered directly from the tank by means of a B-L-B mask (1), and was continued day and night during the period of therapy, except for thirty-minute rest periods five times a day to allow for meals, postural drainage and nursing care. The nasal mask was used in all cases except one. On this last patient, a mouth breather, the oronasal mask was used successfully, in spite of abundant sputum.

Measurements of alveolar oxygen and carbon dioxide concentrations and of arterial carbon dioxide and oxygen values were made at intervals in 5 patients, as shown in table 1. In 2 of the earlier cases studied, alveolar oxygen percentages were below 70 per cent, thus indicating that the inhalation technique was not adequate. There were, of course, numerous practical difficulties in keeping the mask continuously adjusted to patients ill and coughing. Arterial blood studies, on the other hand, done in 5 cases, showed an arterial oxygen saturation over 100 per cent on every examination taken during oxygen inhalation (except one which was 98.9 per cent), indicating a high oxygen pressure in the arterial blood.

Detailed bacteriological analysis of the sputum was also made throughout each patient's course. This included direct examination of the smear and aerobic and anaerobic culture. Quantitative but no qualitative changes in bacterial flora were shown to be produced by oxygen therapy.

CASE REPORTS

The 8 cases are presented in three groups:

Group I: 4 cases with spreading pneumonitis; abscesses, when present, apparently draining effectively through the bronchi.
Group II: 2 cases with non-draining or poorly draining lung abscesses.
Group III: 2 cases whose oxygen therapy was grossly inadequate because of difficulty in its administration.

[1] From the Department of Medicine, College of Physicians and Surgeons, Columbia University, and the Tuberculosis Service, Columbia University Division, Bellevue Hospital, New York City.

[2] Under a grant from the Commonwealth Fund.

Group I

Case 1: J. C., age fifty-two, a white Russian male, worked in Pennsylvania as a hard coal miner for seven years and as a tunnel worker in silicious rock for six years. He had a great increase in the antero-posterior diameter of the chest and other physical evidences of emphysema. Wassermann was positive and there was marked pyorrhoea alveolaris. He had noticed a chronic productive cough for ten years with associated exertional dyspnoea during the last two years. Five weeks before admission he began to experience right-sided chest pain along with increased cough, foul sputum and fever. On entering Bellevue Hospital, May 15, 1940, he was found to be acutely ill. There was dyspnoea at rest and daily temperature to 104°F. Chest X-ray films demonstrated a dense pneumonic consolidation involving the lower half of the right upper lobe and a 3 cm. excavation with fluid level at the third anterior intercostal space. Elsewhere there was diffuse fibro-

TABLE 1

CASE	NAME	DATE	REMARKS	EXPIRED AIR			ARTERIAL BLOOD			
				CO_2	O_2	N_2	CO_2 content	O_2 content	O_2 capacity	O_2 saturation
		1940		*per cent*	*per cent*	*per cent*	*vol. per cent*	*vol. per cent*	*vol. per cent*	*per cent*
1	J. C.	5/29	Wearing O_2 mask	4.5	77.7	17.8	55.5	14.5	14.0	103.5
		5/29	Wearing O_2 mask	3.5	72.6	23.9				
3	M. P.	4/17	Not wearing mask				49.7	13.6	14.3	93.4
		5/2	Wearing O_2 mask				53.4	13.1	12.8	102.5
5	R. B.	5/29	Wearing O_2 mask	4.5	93.4	2.1	46.0	14.7	14.6	101.0
		5/29	Wearing O_2 mask	4.8	92.3	2.9				
6	P. L.	2/6	Not wearing mask				63.4	15.1	17.7	86.1
		2/13	Wearing O_2 mask	6.7	70.4	22.9				
		2/15	Wearing O_2 mask	6.1	53.6	40.3	57.2	17.2	17.4	98.9
		2/20	Wearing O_2 mask	6.1	45.3	48.6	62.2	18.8	18.8	100.0
		2/26	Wearing O_2 mask	4.8	40.7	54.5	60.6	16.9	16.8	101.0
7	F. G.	2/5	Wearing O_2 mask	6.6	77.2	16.2	73.0	16.8	16.7	101.0

sis and emphysema. The aortic shadow was wider than normal and bronchoscopy showed the trachea to be partially obstructed by external pressure in its anterior surface, probably due to the dilated aorta. The patient was treated with bed-rest, sulfathiazole and postural and bronchoscopic drainage without clinical improvement. By the tenth hospital day there had occurred a massive consolidation of the entire right upper and middle lobes with numerous excavations in the former. Sputum continued very foul and averaged 200 cc. daily.

On the eleventh hospital day, oxygen therapy was started by nasal mask. It was then discovered that he was a chronic mouth breather and required the substitution of an oronasal mask covering the mouth. Coincident with this change, the temperature suddenly fell from its previous daily extremes of 102.5°F. to 104°F. down to 100.5°F. or below where it remained. Sputum continued foul and in amount averaged nearly 200 cc. daily for an additional two weeks, then abruptly diminished to approximately 50 cc.

per day. With the change in quantity it likewise became less purulent and foetid. Oxygen therapy was continued for forty-eight days during which the temperature subsided further to completely normal limits, the sputum diminished to less than 30 cc. of non-foul, mucoid material daily, weight gain totalled twenty pounds and the patient felt subjectively well. The last roentgenogram was satisfactory, the middle lobe having cleared, except for residual fibrosis, while the excavated upper lobe had contracted to a portion of its former volume, leaving still some fibrotic shells with dense scarred lung parenchyma about them, but without demonstrable pneumonitis. Following cessation of oxygen therapy the patient's condition remained unchanged and he was discharged from the hospital to a convalescent home on the seventy-eighth hospital day.

Case 2: A. H., a white female, age sixteen, had pneumonia four times at the age of four years, followed by a chronic cough with gradually increasing quantities of sputum. At the age of fifteen she had several small haemoptyses and the sputum became foul. A few months later she was admitted to Bellevue Hospital where bilateral lower lobe bronchiectasis was found and in March, 1939 a left lower lobectomy was performed. Subsequently she was followed in the Out-Patient Department, taking postural drainage at home. She raised about 500 cc. of foul sputum daily. On April 16, 1940, the patient was readmitted to the hospital because of a spreading suppurative process. The left upper lobe showed a massive suppuration with associated multiple abscess cavities, while the lower half of the right lung field contained a dense pneumonia. In addition, she had advanced amyloidosis and the fingers and toes were clubbed. The patient was slightly dyspnoeic at rest.

Because of the extremely far advanced pulmonary suppuration, only conservative measures could be contemplated. High oxygen therapy was begun on the tenth hospital day. Within six days after starting this treatment, the temperature which had previously reached 101°F. to 102°F. daily became normal. The sputum which had measured 400 to 450 cc. diminished to 275 cc. per day. Further decrease took place within three weeks. No foetidity was noted after two weeks, although the patient continued to complain of "foul breath" usually noticed at night. Marked clearing of the pneumonia at the right base occurred. In order to determine what effect withdrawal of oxygen might have, the oxygen mask was discontinued on the thirty-ninth hospital day and again after a week the temperature rose to 101°F. to 102°F. and sputum increased to about 400 cc. daily. There was also much malaise, coughing and a weight loss of three pounds in three weeks. Oxygen therapy was reinstituted on the fifty-eighth hospital day with prompt improvement similar to that obtained before. During the second remission, the temperature was normal, sputum measured about 160 cc. daily and there was a five-pound weight gain in four weeks. Further resolution with almost complete clearing occurred at the right base. No X-ray change could be noted on the left. Oxygen therapy was discontinued again on the eighty-first hospital day. This was followed by a small sputum increase (about 210 cc. daily) and minimal rise in temperature. The patient was discharged to the Out-Patient Department.

Case 3: M. P., a Czechoslovak male, age thirty, was brought to the hospital on August 11, 1939, complaining of cough, bloody sputum and fever for two days. Roentgenograms of the chest demonstrated a pneumonic density on the left between the second and fifth anterior ribs with an abscess cavity at its centre. He was treated with bed-rest, sulfapyridine and bronchoscopic and postural drainage without benefit. A left pneumothorax was induced in November, 1939, preparatory to lobectomy but this was ineffective due to extensive pleural adhesions. Open pneumonolysis was then attempted which was

followed by a foul-smelling empyema necessitating thoracotomy and tube drainage. Later, after additional exploratory surgery, a bronchopleural fistula was discovered. Further therapy included sulfanilamide powder blown through a bronchoscope into the left lower lobe bronchus and zinc peroxide packs in the chest wall wound.

By April 15, 1940, the liver was 3 cm. below the costal margin and there was persistent albuminuria. No congo-red excretion test was done. Roentgenograms revealed a pneumonic involvement of the entire left lower lobe with multiple cavitation. Sputum was extremely foul, wholly purulent and blood-tinged, and had averaged 170 cc. daily for more than two months. Temperature rose to 101°F. to 104°F. daily. There was anaemia in spite of several transfusions and there had been a thirty-one pound weight loss since entry.

High oxygen therapy was instituted on the one hundred and first hospital day. Within three days the temperature had fallen to normal and the sputum became free of blood. This unexpected response was not permanent, however, since the temperature again rose after two weeks, but it never returned to the previous level and usually remained below 100°F. The sputum diminished to 135 cc. daily and then remained at this level. Its odor disappeared temporarily. Appetite and increased food intake produced a four and one-half pound weight gain. Chest roentgenograms indicated there was little or no change in the pulmonary involvement. The bronchopleural fistula remained patent and the pleural exudate persisted but was diminished. Oxygen was administered for a period of sixty days. A few days after withdrawal of oxygen, the patient had a lobectomy of the left lower lobe. He rallied from the operation, but died a week later following profuse haemorrhage from the wound. The left lower lobe removed at operation presented the picture of combined atelectasis, bronchiectasis and multiple abscesses. Autopsy was refused.

Case 4: J. H., a Negro, age twenty-six, developed an acute lung abscess following a drinking bout in May, 1939. In August he was committed to Riker's Island prison hospital where he was considered "moderately ill," with fever to 103.4°F., foul bloody sputum, in quantity between 16 and 20 ounces daily, intermittent cough and undetermined weight loss. X-ray examination then showed a density in the region of the right middle lobe, containing several cavities. Symptomatic therapy was of no immediate benefit, although after two months the patient began to make some improvement. During the last month there he was essentially afebrile. Cough and sputum persisted though the amount and nature of the latter were not recorded. His last roentgenogram showed some decrease in the extent of the density on the right.

On admission to Bellevue Hospital, February 21, 1940, one month after completion of his sentence, a rapid exacerbation had occurred. He was raising 400 to 600 cc. of purulent and extremely foul sputum, cough was constant, temperature 103°F. X-ray and physical findings indicated that there was now a solid pneumonitis with cavitation of the right upper and middle lobes. There was marked anaemia.

Beginning on the eighth hospital day, continuous high oxygen was administered in the routine manner. Within seven days he was afebrile. There was a weight gain of eleven pounds during the first month. Sputum, which during the first few days in the hospital had ranged up to 750 cc., diminished to 60 cc. per day and became nonfoul and mucoid. The cough largely disappeared. Slight blood streaking of the sputum and greater temperature fluctuations occurred following withdrawal of oxygen therapy on the sixty-second hospital day. Due to this, the oxygen was reinstituted after a twelve-day interval and was continued up to date of surgery. Serial roentgenograms demonstrated a gradual clearing of the solid density on the right side leaving a scarred, fibrotic and retracted lung.

On May 23, 1940, the patient had a total right pneumonectomy but died twelve days later. Pathological examination of the resected lung revealed dilatation and sacculation of nearly all bronchi, occasional ulceration of bronchial walls, usually terminating as saccular pockets and abscesses. Some areas of papilliferous proliferation were seen and microscopically, areas of granulation tissue sometimes covered with stratified squamous epithelium were found. Only a few areas of normal alveoli were found interspersed with extensive fibrosis.

Comment

The 4 cases in group I appear clinically to have benefited from administration of high oxygen. This is suggested by a fall in temperature, decrease in amount and foetidity of sputum, gain in weight and general well-being, and in cases 1, 2 and 4, by clearing according to the roentgenograms. In most instances, the temperature depression and decrease in quantity of sputum occurred during the first week of treatment, while the loss of foetidity followed within three or four weeks. It usually required a month or more of oxygen therapy to bring about a substantial improvement and significant change in the X-ray appearance of the lesion. Case 4, the only one in which pathological studies could be made, suggests that healing proceeds as usual by resolution and fibrosis.

The influence of oxygen on pulmonary suppurative disease is depicted graphically in figure 1 (case 2). In this instance, the improvement was manifested by a temperature fall, diminution in amount and foetidity of sputum, gain in weight and improvement in the bronchoscopic findings. Relapse occurred promptly when oxygen was withdrawn, but the patient improved again when it was reinstituted.

The improvement noted in these cases occurred in spite of longstanding suppurative disease, in all but case 1 of many months' duration.

Group II

Case 5: R. B., age forty-eight, a colored longshoreman, had complained of a chronic cough for many years in addition to "pneumonia" on the right side in 1935. During the last five months he had noticed weakness due to repeated "colds." Examination on entry revealed solid pneumonitis of the right upper lobe without X-ray evidence of excavation. The aorta was dilated and Wassermann reaction was positive. High oxygen therapy was begun on the twenty-third hospital day and was followed by a temporary drop in temperature from 100.5°F. to normal and by a slight diminution in daily sputum output. This, however, was interrupted by two severe febrile episodes each lasting about five days and occurring during the next month. These were associated with extreme toxaemia, increased sputum and by extensive necrosis and excavation of the right upper lobe. On the sixty-seventh day in the hospital, the oxygen was discontinued and the patient had open surgical drainage of the cavities. A roentgenogram just prior to surgery showed little change, except for obliteration of cavity outlines probably due to retention of secretions by a blocked bronchus. Six months after operation the patient felt well. There was some residual infiltration and fibrosis at the previous site but no definite cavity. He was discharged to the clinic.

Case 6: P. L., a white male, age thirty-nine, had had "pneumonia" in 1933 which followed submersion in the Hudson River and had developed a right-sided lung abscess one

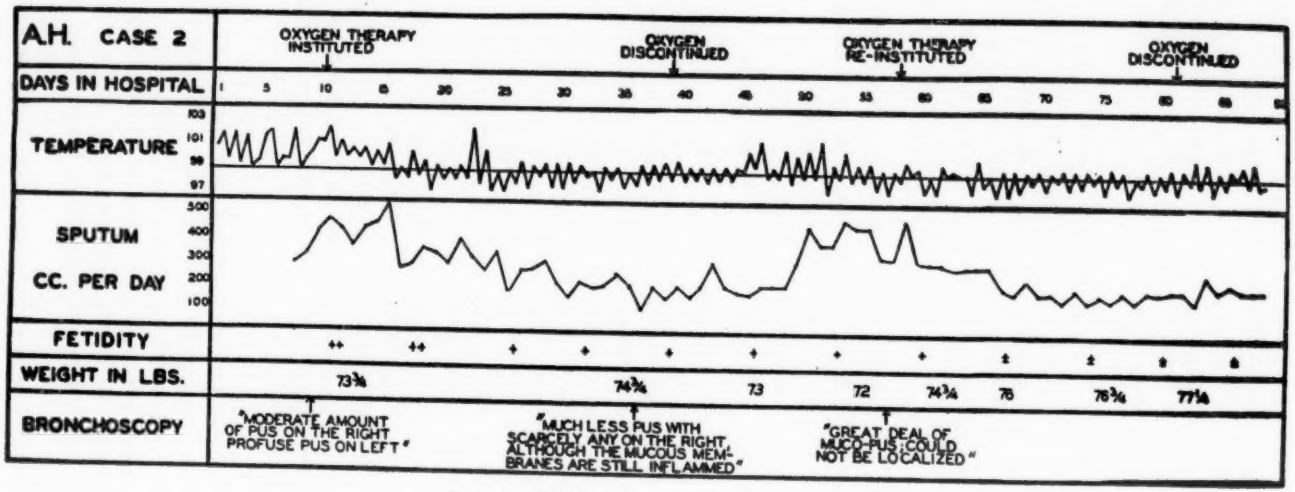
A.H. CASE 2
OXYGEN THERAPY INSTITUTED
OXYGEN DISCONTINUED
OXYGEN THERAPY RE-INSTITUTED
OXYGEN DISCONTINUED
DAYS IN HOSPITAL
1 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85
TEMPERATURE
103
101
99
97
SPUTUM CC. PER DAY
500
400
300
200
100
FETIDITY
++ ++ + + + + + + ± ± ± ±
WEIGHT IN LBS.
73¾ 74¾ 73 72 74¾ 76 76¾ 77¼
BRONCHOSCOPY
"MODERATE AMOUNT OF PUS ON THE RIGHT PROFUSE PUS ON LEFT"
"MUCH LESS PUS WITH SCARCELY ANY ON THE RIGHT ALTHOUGH THE MUCOUS MEMBRANES ARE STILL INFLAMMED"
"GREAT DEAL OF MUCO-PUS; COULD NOT BE LOCALIZED"

FIG. 1. Clinical chart of A. H. (case 2)

year later complicated by empyema. In 1936, a rib resection and surgical drainage of the abscess cavity was done. Residual cough and sputum persisted in spite of postural drainage practiced at home.

On admission, February 5, 1940, the patient was seriously ill. A cavity surrounded by dense pneumonitis and containing a fluid level was noted at the site of the previous abscesses. The temperature remained above 102°F.; foul purulent sputum amounted to 400 cc. daily; the fingers were clubbed; the lips were cyanotic. A fluctuant mass associated with exquisite tenderness above the site indicated that the abscess had also ruptured through the pleurae and was bulging outward through the soft tissues, a so-called sacculated *empyema necessitatis*.

High oxygen therapy was begun on the third hospital day along with bronchoscopic and postural drainage. On the sixth day the patient apparently established drainage from his abscess through the bronchus, coughed up 400 cc. of pus within a few hours and promptly experienced a temperature depression to below 100°F. In four days the temperature fell to normal and remained so. A fleeting pneumonitis on the left was noted in one roentgenogram during the oxygen trial period. Within two weeks, the sputum had diminished to 60 cc. daily and there had occurred a six-pound weight gain. Oxygen was discontinued on the twenty-seventh hospital day when the patient was symptomatically well except for 50 cc. of mucoid sputum per day. The pneumonitis about the cavity had completely cleared leaving a fibrotic annular shadow at the cavity site. After cessation of oxygen, the temperature fluctuations became greater, reaching 100°F. on most days, and the sputum increased to 110 cc. daily while the X-ray appearance remained unchanged. Cautery pneumonectomy to remove damaged parenchyma at the site of the abscess was contemplated when the patient left the hospital against advice.

Comment

Both of these patients exhibited the clinical evidence of poorly draining cavities of the right lung. The deciding factor in one of these cases was the spontaneous rupture of the abscess into a bronchus. Any effect due to oxygen therapy was problematical, although in case 6 the cyanosis was promptly abolished and there was some return of symptoms after withdrawal of oxygen.

Group III

Case 7: F. G., a white male, age forty-five, had had a chronic cough since childhood, "pleurisy" in 1919, "lobar pneumonia" in 1929, bronchopneumonia in 1930 and an undiagnosed peripheral lesion demonstrated by X-ray on the right in 1937. He was a heroin addict and a chronic alcoholic, having cirrhosis of the liver and associated dietary deficiency. He entered the hospital on November 19, 1939 with multiple lung abscesses of the left upper lobe.

During his hospital stay there was a progressive increase in sputum, fever and weight loss with some spread of the pneumonitis surrounding existing abscess cavities. High oxygen therapy was begun on the seventy-second hospital day but was discontinued after only seven days. The patient had a pronounced nasal obstruction and in spite of the attempted coöperation breathed almost entirely by mouth. Substitution of the oronasal mask was not tolerated because of interference with the raising of large quantities of sputum. During the oxygen trial period there was some increase of left pleural pain and a slight elevation of temperature but a decrease of 100 cc. in the daily sputum output. At the same time, there was an increase in the size of the pneumonic density

about the excavations. Two weeks later, he was transferred to a hospital for chronic diseases.

Case 8: P. S., age thirty-four, a white male, a chronic alcoholic developed "pneumonia" six months before admission. Since that time the sputum had remained foul and purulent and amounted to a cupful daily. A flare-up one week before, characterized by chills, fever and increased cough and sputum, brought him to the hospital. Chest roentgenograms demonstrated a lung abscess containing a fluid level in the left upper lobe. Treatment included bronchoscopic and postural drainage and after the tenth hospital day high oxygen therapy with mask. The patient refused to coöperate, however, and was often discovered walking about or lying in bed without the mask. Several additional cavities appeared during the first month, but later, coincident with more reasonable coöperation, there was a gradual recession of the surrounding pneumonitis and coalescence of several small cavities in association with diminished symptoms.

On the fifty-second hospital day, the patient experienced fever to 103°F., but without change in amount or nature of sputum or in appearance of the roentgenogram. He was then transferred to the Surgical Division for open drainage of his cavity. Following operation the symptoms disappeared and he was discharged to the Out-patient Department.

Comment

Both of these cases must be considered failures as regards the clinical response to oxygen therapy. In one instance, the procedure did not have an adequate trial and in the other there was poor coöperation.

DISCUSSION

While it is difficult to draw conclusions from a few clinical case reports, especially when the pathological condition is chronic and no cure is obtained, there appears to be little doubt that the first 4 of the above patients with chronic putrid lung infections and spreading pneumonitis were benefited clinically during the course of prolonged oxygen therapy. Clinical improvement was manifested by fall in the temperature, decrease in the amount and foetidity of sputum, gain in weight and general well-being, and in some instances by clearing of the X-ray signs of disease.

The mode of action of oxygen is not clear. It is known that the administration of pure oxygen may increase the arterial blood oxygen load in normal individuals by about 12 per cent over that obtained while breathing air. This is brought about by the complete saturation of the haemoglobin and by an increment in the amount of oxygen carried in simple solution by the plasma (2). In addition, most patients with chronic suppurative pneumonia have some degree of arterial oxygen unsaturation while breathing air. This is probably due to perfusion by blood of unaerated lung areas or to an impairment in the diffusion of oxygen across the alveolar membranes. The latter may result from oedema or thickening of the membrane. In such cases, oxygen administration raises the pressure of the gas in the alveoli and increases its rate of diffusion across their walls (3). Whatever be the mechanism, 5 patients in our series for whom blood oxygen saturation was determined during high oxygen treatment showed

a percentage increase in oxygen carried by a unit volume of arterial blood which ranged between 14.3 and 22.5 per cent.

In this respect another factor may be of importance. Due to the shape of the oxygen dissociation curve, the oxygen tension in the tissues increases far out of proportion to the increase in arterial blood oxygen saturation when the upper levels are considered. If blood flow remains constant this suggests that a considerable increase in tissue oxygen tension may follow oxygen administration to these patients. In discussing pneumonia, Binger states that, while this has no specific effect on the invading microörganisms, it tends to restore to its normal state the internal environment of the host (4). While it may stimulate greater resistance to infection on the part of the tissues, there is probably no direct effect on the invading anaerobes which are deeply buried in necrotic tissue. For the same reason, oxygen diffusion into the abscess cavity is probably ineffective.

Other investigators have had some success with oxygen therapy in pulmonary infections. Its value in pneumonia is well established. Boothby and Haines report a reduction of fever in pneumonia following oxygen administration in addition to the more commonly known effects (5). Most authors, however, consider oxygen of value in so far as it can relieve or abolish anoxaemia. It may aid the tissues to resist further bacterial advance by increasing the oxygen tension in ischaemic or poorly capillarized areas of the lung.

The tentative conclusion which is suggested by this limited series of clinical studies is that in cases with putrid lung infection with spreading pneumonitis, in which the actual abscesses are draining more or less adequately, high oxygen therapy administered with a suitable face-mask can be used as an adjuvant measure for symptomatic relief, and will provide such relief in a considerable proportion of instances. In those cases in which surgery must be delayed or the severity of the disease prevents more active measures, oxygen therapy may be helfpful in preparation for operation. This treatment cannot in any sense be considered as a cure.

Finally, it is important to note that close follow-up failed to reveal in this series any manifestation of oxygen intoxication in spite of persistently high concentrations of oxygen in the inhaled atmosphere.

SUMMARY

1. Eight cases of chronic suppurative pneumonia with foul sputum have been treated with high oxygen atmospheres over long periods of time. Four cases with spreading pneumonitis were apparently improved by this treatment. The most significant change observed was a more or less complete disappearance of foetidity and a reduction in the volume of expectoration. One patient, with inadequately draining abscesses and two patients who were unable to coöperate in taking the treatment were not improved by oxygen. One of the patients with inadequate drainage from his abscess improved promptly following spontaneous establishment of drainage.

2. Prolonged high-oxygen therapy is suggested as an adjuvant for symptomatic relief in this form of pulmonary disease, particularly if surgical measures must be delayed or are not feasible.

3. No deleterious effect of high oxygen therapy was noted following prolonged and almost continuous treatment.

SUMARIO

1. Ocho casos de neumonía supurada crónica con fetidez del esputo fueron tratados en una atmósfera saturada de oxígeno durante períodos prolongados. Cuatro casos en que había neumonitis en vías de propagación, mejoraron aparentemente con dicho tratamiento. La alteración más significativa consistió en una desaparición más o menos completa de la fetidez y disminución del volumen de esputo. En cambio no mejoraron con el oxígeno uno enfermo en que había abscesos que supuraban inadecuadamente y otros dos que no pudieron cooperar en el tratamiento. Uno de los enfermos en que era inadecuada la canalización del absceso mejoró prontamente al establecerse espontáneamente el drenaje.

2. Propónese la hiperoxigenoterapia prolongada como coadyuvante del alivio sintomático en esta neumopatía, en particular si hay que dilatar las medidas quirúrgicas o no resultan factibles.

3. No se observó efecto nocivo de la hiperoxigenoterapia ni aun con un tratamiento prolongado y casi continuo.

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ELECTROPHORESIS OF SERUM[1,2,3]

Serum Proteins in Tuberculosis and Other Chronic Diseases

FLORENCE B. SEIBERT AND J. WALTER NELSON

It has been shown previously (1) that a rise in one of the globulin fractions, namely the beta-globulin, occurred in the sera of 10 tuberculous rabbits. The regularity with which this phenomenon occurs is emphasized in the study here reported on 15 additional rabbits. In this paper it will be pointed out that there may even exist a difference in the tendency to produce this fraction of the serum by rabbits of different constitutional heredity. This report will be concerned chiefly with recording the actual changes in the serum which occur with progress of the disease and the significance of these changes will be considered in the future.

The rabbits whose numbers are preceded by the letter A belong to a family known to be naturally resistant to tuberculosis, and those with the letters C or F belong to families of rabbits known to be naturally susceptible to the disease. We are indebted to Dr. Max B. Lurie for furnishing us sera from these rabbits, on which he has recorded extensive data (2). Numbers following the letters indicate the generation of inbreeding by Doctor Lurie. For example, F4 and F5 represent the fourth and fifth generations of the F family, and A5, A6, A7 represent the fifth, sixth and seventh generations of the A family respectively. Those rabbits whose numbers were preceded by no letter had been obtained on the market.

All of the analyses recorded were obtained by means of the electrophoretic technique of Tiselius (3), using the Svensson modification (4) of the Philpot optical arrangement. Always 4, and in some cases 5 exposures at 25°, 30°, 35°, 40° and occasionally 45° angles were made of the descending components. The curves were then enlarged 7.5 times and the areas under the curves measured with the planimeter. From these areas the concentrations of the various serum constituents were calculated and recorded as the average of the 4 or 5 determinations. The sum of these concentrations gave the total concentration for the serum proteins and from this the percentage of the various components was calculated and recorded as such.

SERUM CHANGES IN TUBERCULOSIS IN RABBITS

Table 1 gives at first the average and also the ranges of values for total protein concentration and percentage of this total protein as albumin, alpha-, beta-, and gamma-globulin in 35 normal rabbits. Using these figures as the normal values

[1] Presented before the Medical Section at the 38th annual meeting of the National Tuberculosis Association, Philadelphia, Pennsylvania, May 8, 1942.

[2] From the Henry Phipps Institute of the University of Pennsylvania, Philadelphia.

[3] Aided by a grant from the Committee on Medical Research of the National Tuberculosis Association.

it can be seen that in all of the 11 tuberculous rabbits there was a great decrease in albumin, and an increase in beta-globulin occurred, which reached two to three fold by the time of terminal tuberculosis. There are recorded in this table only those rabbits on which a blood sample was obtained shortly before death and in which at autopsy uncomplicated tuberculosis was found. Figure 1 shows the electrophoretic diagrams of the sera of 5 of these rabbits. From left to right these represent sera as follows: normal, before infection; intermediate, some time after infection; and terminal, shortly before death. The first 4 (table 1) and last 2 rabbits were inoculated intracutaneously with 0.2 mg. Ravenel strain of bovine tubercle bacilli, the next 3 intravenously with 0.001 mg. and the next 2 intravenously with 0.000,1 mg. of the same strain. In this study there

TABLE 1

Serum changes in terminal tuberculosis in rabbits

RABBIT NUMBER	DAYS AFTER INOCULATION	TOTAL PROTEIN CONCENTRATION	PER CENT OF TOTAL PROTEIN AS			
			Albumin	Globulins		
				Alpha	Beta	Gamma
		per cent				
Normal (35)		5.6	75.0	2.4	10.8	11.9
(Range)		4.4–6.9	68.4–81.5	0–4.7	7.9–15.1	7.9–15.5
#62	86	7.4	55.6	4.5	24.9	15.1
#60	132	6.3	56.1	4.8	23.8	15.3
#39	238	5.2	50.2	6.1	22.4	12.8
#63	278	5.8	53.6	5.6	25.3	15.5
#171	138	5.6	46.2	5.7	29.7	18.3
#161	144	5.0	33.8	18.0	26.9	21.3
#172	147	6.4	41.1	11.4	26.0	21.6
F4-62	83	6.0	33.5 20.3	15.8	21.4	9.1
F5-19	125	7.6	31.0	33.0	22.0	13.8
A5 = 5*	771	3.3	50.0	11.0	27.2	11.8
A5 = 19*	651	5.8	53.1		31.8	15.1

* Vaccinated.

were at least 12 more infected rabbits which showed a definite rise in the beta-globulin fraction, but they are not recorded because a bleeding was obtained not later than a month or more before death, or because they died from intercurrent infection. In fact there was none of the 25 rabbits studied which did not show some rise in the beta-globulin fraction following infection with tubercle bacilli.

In some rabbits, especially numbers 161, 172, F4–62, F5–19, A5=5, there occurred, in addition to the rise in beta-globulin, a significant rise in the alpha-globulin fraction. The exact explanation of this fact is not clear at the present time. The electrophoretic diagrams of 4 of these rabbits are shown in figure 2. The gamma-globulin also rose in many of the rabbits, but not in all cases.

It is obvious, then, that an increase in the beta-globulin fraction and a cor-

responding decrease in albumin, are the most consistent changes to be noted in the serum of rabbits during the development of tuberculosis. It was interesting, then, to note how soon after inoculation changes in these components could be detected.

Table 2 shows that in many rabbits a definite rise occurred in the beta-globulin fraction as early as ten days to two weeks following infection. Ob-

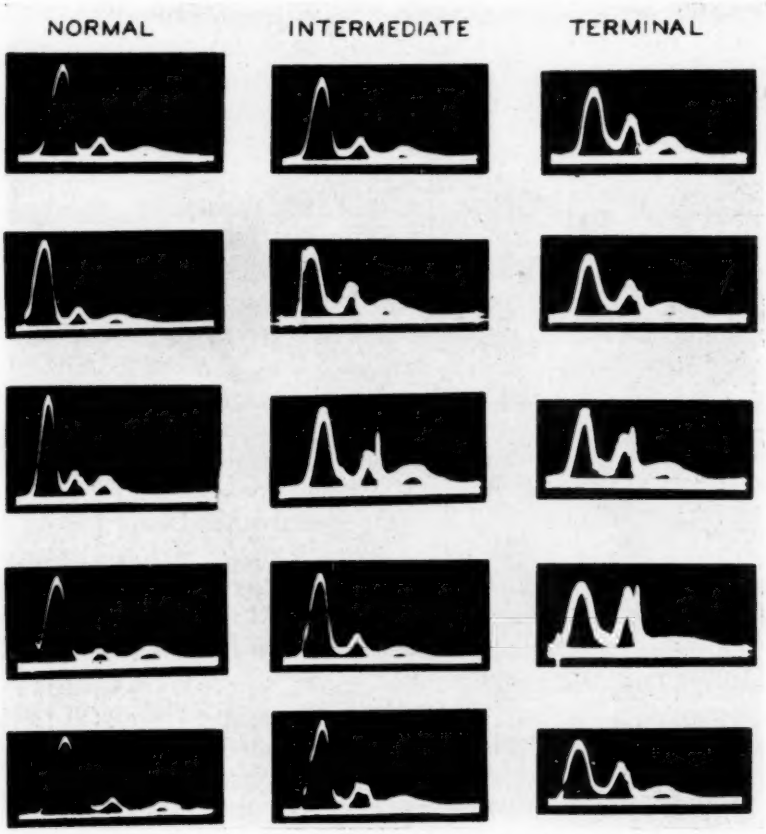

FIG. 1. Electrophoretic diagrams of sera of rabbits before infection, after infection and shortly before death. The largest and fastest component, at the left in each diagram, represents albumin. Next, in order of mobility, is the alpha-globulin, distinctly seen in only a few cases, then beta-globulin and, slowest, gamma-globulin.

viously it was not possible with this technique to make daily tests and in some cases shorter interval bleedings might have revealed an earlier rise, as for example, in the case of F4–62, 60, 63, etc. In all cases the albumin showed a corresponding decrease. The changes in the gamma-globulin fraction, however, were not at all consistent.

Further indication of the importance of the beta-globulin fraction in tuberculosis lies in the fact that the sera of rabbits belonging to the family A, known to

have a high natural resistance to tuberculosis, normally have a lower beta-globulin than those belonging to families C and F, known to be highly susceptible to the disease. Table 3 shows the average analyses and the ranges on 11 resistant, 10 susceptible and 14 market rabbits. The beta-globulin was noticeably lower in the resistant than in the susceptible rabbits and the gamma-globulin was higher. Statistical analysis of these values shows (table 4) that the difference in the beta-globulin fractions is highly significant, whereas the

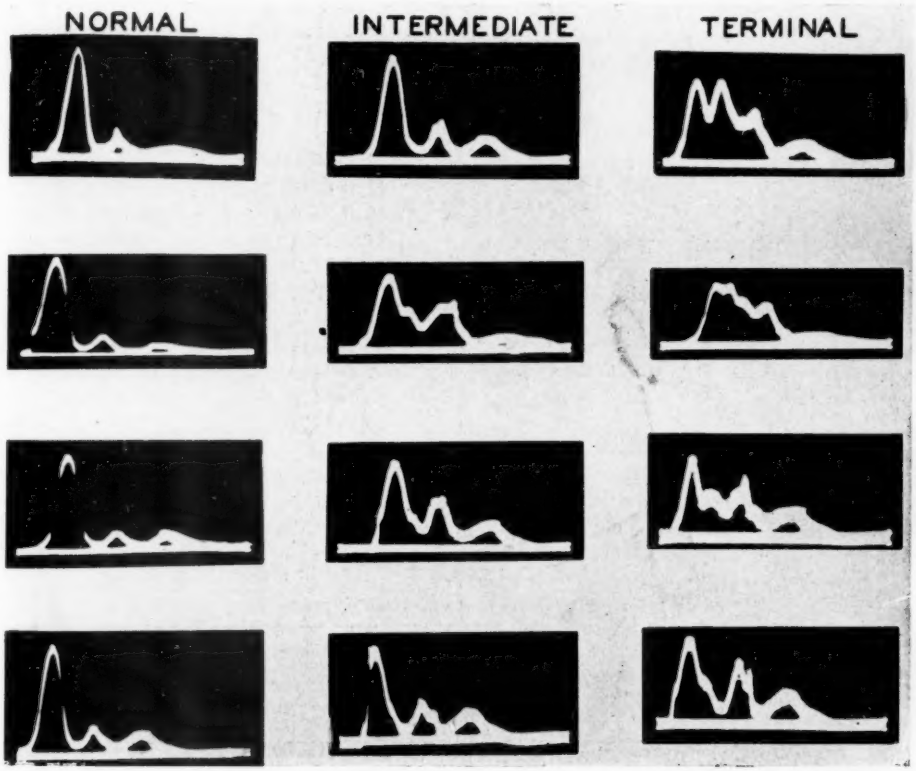

FIG. 2. Electrophoretic diagrams of sera of rabbits before infection, after infection and shortly before death. The alpha-globulin peak, second to the left in the terminal stage, has risen from practically nothing before infection. In all cases the beta-globulin, second peak to the right, has also become much larger.

difference in the gamma-globulin is of comparatively little significance. The sera of the market rabbits appeared to be more like susceptible rabbits in their beta-globulin and more like resistant rabbits in their gamma-globulin content.

SERUM CHANGES IN TUBERCULOSIS IN MAN

Obviously it is not possible to control investigations on human tuberculous sera as carefully as in the case of experimental tuberculosis in rabbits and, therefore, the conclusions cannot be as definite nor the results as instructive. An

attempt will, therefore, be made merely to record some of results so far obtained and to reserve conclusions until more data are accumulated. Table 5 gives the concentrations for the serum protein constituents of 12 persons considered to

TABLE 2

Serum changes in early tuberculosis in rabbits

RABBIT NUMBER	DAYS AFTER INOCULATION	CHANGES RFOM NORMAL IN GLOBULINS	
		Beta	Gamma
C4S-26	38	10.3–16.0	12.4–11.4
C4S-28	14	9.7–18.5	11.3– 2.8
C 5-2	59	11.8–15.6	10.7–16.1
C 5-31	27	12.1–23.1	10.3–12.4
C 5-43	13	12.4–25.6	9.8–16.1
F 4-48	14	11.7–17.1	12.1–11.8
F 4-62	63	11.9–32.8	9.4–11.7
F 5-19	14	11.8–27.4	10.8–13.1
F 6 = 6	14	11.3–15.9	7.9– 7.9
F 6 = 7	27	11.3–17.9	9.5–10.0
A 6 = 6	38	8.8– 9.3	13.2–17.5
A 7 = 8	31	10.6–14.4	12.2–16.1
39‡	10	10.2–14.7	14.8–14.4
60‡	68	11.9–14.0	10.1–12.7
62‡	10	8.9–14.3	13.3–11.2
63‡	100	12.7–17.8	12.0–14.7

All rabbits inoculated intravenously with 0.000,1 mg. Ravenel bovine strain tubercle bacillus, except those marked with ‡.

‡ Inoculated intracutaneously with 0.2 mg. Ravenel bovine tubercle bacillus.

TABLE 3

Composition of normal rabbit sera

	TOTAL PROTEIN CONCENTRATION	PER CENT OF TOTAL PROTEIN AS			
		Albumin	Globulins		
			Alpha	Beta	Gamma
	per cent				
Resistant Family *A*					
11 (Average)	5.7	76.1	3.0	9.3	11.6
(Range)	5.0–6.5	71.1–81.5	0–4.7	7.9–11.5	9.3–15.4
Susceptible families *C* and *F*					
10 (Average)	5.3	75.7	2.2	11.9	10.2
(Range)	4.4–6.0	73.6–78.9	0–3.3	9.7–15.1	7.9–11.3
Market Families					
14 (Average)	5.8	73.4	2.0	11.3	13.3
(Range)	4.6–6.9	68.4–76.8	0–4.3	9.2–13.5	10.1–15.5

be normal from the clinical standpoint. The table also shows that in all cases of tuberculosis the percentage of albumin decreased and the decrease was greater the more advanced the stage of the disease. Figure 3 shows that the electro-

phoretic diagrams of representative sera from this series change progressively from the normal with advance in tuberculosis.

In contrast to the rise in the beta-globulin in experimental tuberculosis in the rabbits, the consistent change in human sera was in the gamma-globulin fraction, and the rise seems to be greater the more advanced the stage of tuberculosis.

In many cases there was also a significant rise in the alpha-globulin. For example, there was a rise in this fraction in A.H. in the last two bleedings, when the clinical course was showing a decline. In R.B. the alpha-globulin decreased and simultaneously the clinical course was showing improvement. In this case pneumothorax had been started. L. V. showed marked improvement at the

TABLE 4

Resistant and susceptible normal rabbits

	PER CENT OF TOTAL SERUM PROTEIN AS			
	Beta globulin		Gamma globulin	
Family	A	C + F	A	C + F
Number rabbits	11	10	11	10
	11.5	15.1	15.4	12.1
	10.6	12.4	13.9	11.3
	10.3	12.1	13.2	10.8
	9.2	11.9	12.2	10.7
	9.1	11.8	11.5	10.3
	8.9	11.8	11.3	10.2
	8.9	11.7	10.6	9.8
	8.8	11.3	10.6	9.5
	8.4	11.3	9.9	9.4
	8.4	9.7	9.4	7.9
	7.9		9.3	
Average per cent	9.3	11.9	11.6	10.2
Standard deviation	±1.04	±1.27	±1.82	±1.096
Ps	1.000		0.970	

time of the last bleeding and the alpha-globulin, and gamma-globulin as well, were decreasing. S. H., who died within a few days of the bleeding, had an acute toxaemic course with extensive cavitation of the lungs, and there was no generalization. None of the minimal cases showed a high alpha-globulin.

The last column in table 5 shows that the "x component," discussed in the previous paper (1), which has a mobility slightly greater than albumin, in general seemed to become more prominent when the clinical course was declining and to diminisb in amount and even disappear when there was improvement.

At the end of the table are given the analyses on two pleural fluids taken from tuberculous patients. It is noteworthy that the protein pattern of these fluids is very similar to that of serum. In the case of W. J., a sample of serum taken simultaneously differed very little from the pleural fluid except in total protein

TABLE 5

Composition of human sera in tuberculosis

PATIENT	TOTAL PROTEIN CONCENTRATION	PER CENT OF TOTAL PROTEIN AS				X = COMPONENT	DATE OF BLEEDING	REMARKS
		Albumin	Globulins					
			Alpha	Beta	Gamma			
	per cent							
Normals (12)...	6.7	67.4	5.4	11.5	15.7			
(Range).....	5.0–8.1	63.7–71.4	3.4–8.3	7.8–15.2	12.3–19.3			
Minimal								
C. E. B.....	6.8	59.5	6.0	13.4	21.0	−		
W. S.....	6.3	59.2	5.6	11.9	23.4	+		
J. H.....	8.6	58.1	6.4	16.7	18.9	−	1- 8-42	
	7.8	58.7	6.9	13.3	21.2	+	2- 2-42	Clinical improvement
Far advanced								
L. V.....	7.2	58.6	6.5	14.3	20.6	+	4-28-41	
	6.5	58.9	5.9	15.9	19.3	+	10-14-41	
	8.1	58.7	7.1	13.5	21.0	+	10-31-41	
	6.6	61.8	6.6	13.8	17.9	−	3-26-42	Clinical improvement
R. B.....	6.5	54.8	9.0	13.6	22.5	++	5- 5-41	
	7.1	53.5	7.6	15.2	23.7	+	10-14-41	
	9.0	52.9	8.1	15.5	23.6	++	10-31-41	Improvement; pneumothorax started
	9.0	55.1	7.7	14.6	22.6	+	2-11-42	
	6.4	56.2	6.8	14.2	22.7	−	4-13-42	
A. H.....	7.6	53.7	4.1	13.7	28.6	−	4-26-41	Disease four years
	7.8	53.0	5.8	13.8	26.9	+	10-13-41	
	7.3	52.8	5.1	15.2	26.9	+	11- 3-41	Not doing well
	7.9	52.0	7.1	12.9	28.0	++	2-16-42	
	7.4	51.3	8.6	11.8	28.4	++	4- 8-42	Much worse
Terminal								
J. H.....	7.3	43.0	6.8	16.8	33.4	+		
S. H.....	7.4	42.7	9.4	10.2	37.7	++		Extensive cavitation (localized in lungs) (no generalization)
W. J.—Serum	8.6	54.0	5.8	12.8	27.4	+		3-11-42
W. J.—Pleural fluid....	4.3	58.3	5.2	14.0	22.6	+?		3-11-42
W. J.—Pleural fluid....	9.4	58.8	5.8	13.4	21.9	+		3- 3-42
B. W.—Pleural fluid....	5.6	54.3	7.0	12.0	26.7	−		3- 3-42
B. W.—Pleural fluid....	4.5	49.7	2.9	12.3	35.2	−		3-17-42

concentration. Figure 4 shows the close correspondence between the two, as demonstrated by electrophoresis.

SERUM CHANGES IN SARCOIDOSIS

Because of the suggestion (5) that sarcoidosis may be a noncaseating tuberculosis, it was interesting to observe by electrophoresis the serum changes in cases

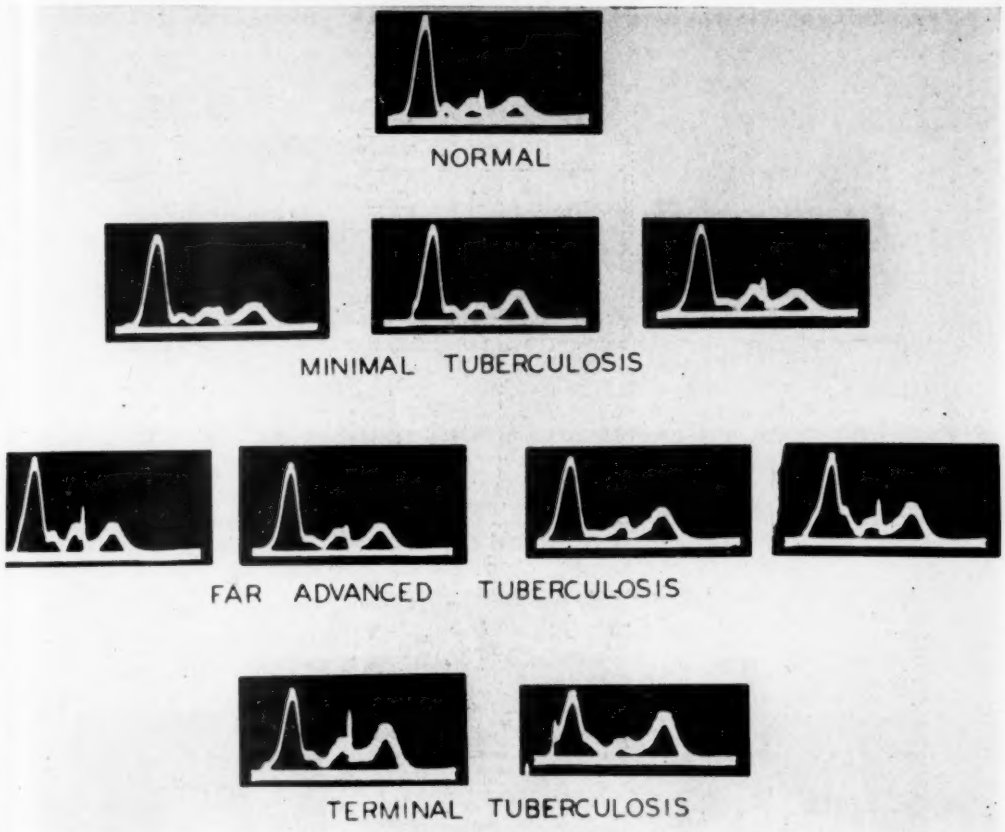

FIG. 3. Electrophretoic diagrams of human sera. The cases of far advanced tuberculosis are, in order from left to right, L. V., R. B. and A. H., at the time of first bleeding, and A. H. at the time of the last bleeding. In this last diagram note the "x-component" which appears as a bend in the left side of the albumin peak, and also the increased alpha-globulin, coming from the right side of the albumin curve. The curves for terminal tuberculosis are those of J. N. at the left and S. H. at the right.

of sarcoid. Previous investigators including Harrell (6), Longcope (7), Gutman *et al.* (8) and others have demonstrated that the globulins are usually high. The last mentioned authors, using the Howe precipitation method, showed that the rise was chiefly in the euglobulin and pseudoglobulin-I fractions.

Table 6 and figure 5 demonstrate that the rise in the globulins was mainly in the gamma-fraction. Some of this fraction was isolated from serum M. M.

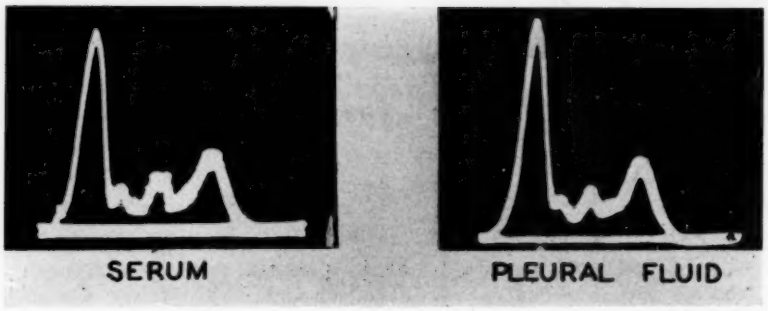

FIG. 4. Electrophoretic diagrams of a serum and a pleural fluid taken simultaneously

TABLE 6

Composition of sera in sarcoidosis

PATIENT	TOTAL PROTEIN CONCENTRATION	PER CENT OF TOTAL PROTEIN AS				TUBERCULIN TEST
		Albumin	Globulins			
			Alpha	Beta	Gamma	
	per cent					
Normals (12)	6.7	67.4	5.4	11.5	15.7	
(Range)	5.0–8.1	63.7–71.4	3.4–8.3	7.8–15.2	12.3–19.3	+
M. M.*	8.1	33.3	6.8	24.4	35.6	+
E. S.	7.9	53.8	5.5	13.3	27.7	−
E. M.	9.0	48.4	6.1	18.5	27.0	−
J. G.	8.8	59.1	6.2	11.8	23.1	−
C. H.	6.9	57.6	5.5	12.3	22.1	−
L. G.	7.5	55.4	4.7	14.6	25.3	+ (weak)

* Diagnosis confirmed by biopsy.

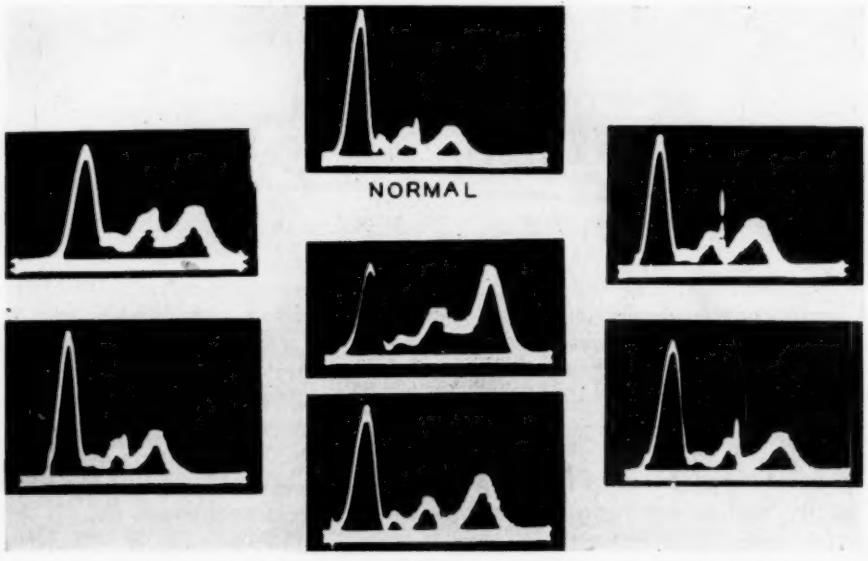

FIG. 5. Electrophoretic diagrams of sarcoid sera. The two sera underneath the normal were from M. M. and E. S., respectively, the 2 cases proven by biopsy. Note the high gamma-globulin in all cases.

by electrophoresis in rather pure form. When it was tested for anticutin activity in tuberculous guinea pigs, none could be demonstrated. Furthermore, none of the whole sera, when tested similarly, showed any neutralizing power for tuberculin.

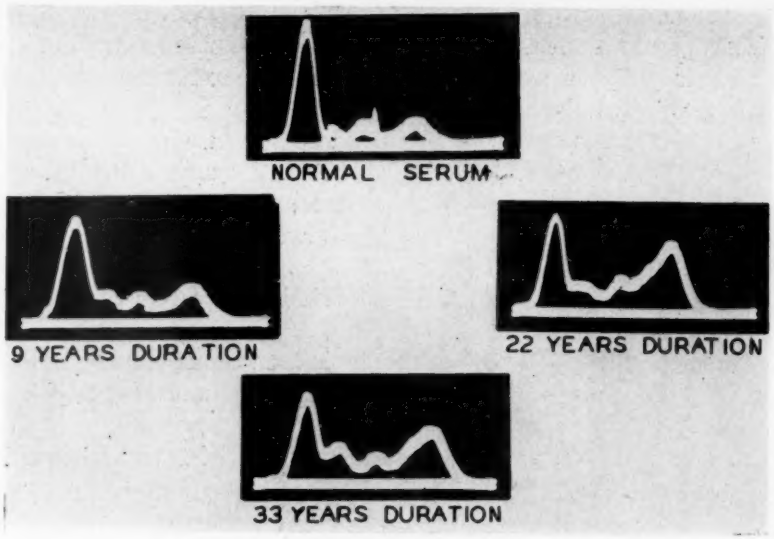

FIG. 6. Electrophoretic diagrams of sera from lepers

TABLE 7

Composition of sera in leprosy

PATIENT	TOTAL PROTEIN CONCENTRATION	PER CENT OF TOTAL PROTEIN AS				DURATION OF DISEASE
		Albumin	Globulins			
			Alpha	Beta	Gamma	
	per cent					*years*
Normals (12).....	6.7	67.4	5.4	11.5	15.7	
(Range).....	5.0–8.1	63.7–71.4	3.4–8.3	7.8–15.2	12.3–19.3	
#92	8.4	56.0	9.8	10.3	23.7	12
#121	7.4	37.5	15.0	9.7	37.7	33
#122	8.0	36.0	10.5	10.5	43.0	22

SERUM CHANGES IN LEPROSY

Table 7 and figure 6 show that in advanced leprosy rises in the gamma- and alpha-globulins occur. The sera used were obtained from patients in Culion, P. I., through the kindness of Dr. John H. Hanks.

SUMMARY

Studies by means of electrophoresis were made of the serum proteins of rabbits and human beings. In experimental tuberculosis in rabbits a consistent decrease

in the percentage of serum albumin and a rise in the beta-globulin always occurred. These changes were proportional to the stage of the disease. In some rabbits a significant rise occurred also in the alpha-globulin. Changes in the gamma-globulin were irregular.

In many rabbits a rise in the beta-globulin could be detected as early as ten days to two weeks following inoculation.

A significantly lower beta-globulin percentage was noted in uninfected rabbits belonging to a family known to be naturally resistant to tuberculosis, in contrast to rabbits from naturally susceptible families.

In several cases of human tuberculosis abnormal values for the serum proteins were observed which seemed to parallel the clinical course of the disease. The conspicuous changes were a decrease in albumin, a rise in the gamma- and alpha-globulins, and the appearance of an unknown component, which is under investigation (x-component).

Two pleural fluids appeared to be very similar to serum in their protein pattern.

In 6 cases of sarcoidosis a conspicuous rise in the gamma-globulin of the serum was noted. Anticutins could not be demonstrated in these sera nor in a gamma-fraction isolated from one of them.

In 3 advanced cases of leprosy a great rise in the alpha- and gamma-globulin constituents occurred.

SUMARIO

Hiciéronse estudios electroforéticos de las proteínas séricas de conejos y de seres humanos. En la tuberculosis experimental del conejo observóse siempre disminución del porcentaje de sero-albúmina y elevación de la globulina-beta, guardando esas alteraciones relación con el período de la dolencia. En algunos conejos observóse también un aumento significativo de la globulina-alfa, pero las alteraciones de la globulina-gama fueron irregulares.

En muchos conejos podía observarse un aumento de la globulina-beta ya de 10 días a dos semanas después de la inoculación.

En los conejos no infectados que pertenecían a una familia conocida por su resistencia natural a la tuberculosis, observóse un porcentaje significativamente menor de globulina-beta que en los procedentes de familias naturalmente susceptibles.

En varios casos de tuberculosis humana observáronse cifras para las proteínas séricas que parecían remedar la evolución clínica, consistiendo las alteraciones más notables en disminución de la albúmina, aumento de las globulinas gama y alfa y aparición de un componente desconocido (x) que sigue en estudio.

Dos ejemplares de líquido pleural aparecieron muy semejantes al suero en lo tocante al tenor de proteínas.

En seis casos de sarcoidosis notóse un aumento notable de la globulina-gama del suero. No pudieron observarse anticutinas en estos sueros ni en la fracción gama aislada de uno de ellos.

En tres casos avanzados de lepra sobrevino un gran aumento de las fracciones de globulinas alfa y gama.

Appreciation is expressed to Drs. Horace R. Getz, Harold L. Israel, Samuel C. Stein and William H. Rodgers for the sera from patients. We acknowledge the assistance of Mabel V. Seibert and also of Dora Duchovnay, assistant from the National Youth Administration, in measuring the electrophoretic diagrams.

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EXPERIMENTAL PULMONARY TUBERCULOSIS IN THE DOG[1,2]

Reinfection

F. D. GUNN, M. A. MILLS, C. C. SHEPARD AND E. E. BARTH

Many attempts have been made to reproduce experimentally in laboratory animals the various forms of lesions which we recognize as typical of pulmonary tuberculosis in man. These have been successful only to the extent that the rapidly progressive bronchopneumonic lesions with early extension to lymph nodes and wide-spread haematogenous foci in the viscera of the more susceptible animals bear a sufficiently close resemblance to those in rapidly progressive disease, sometimes found in human infants and occasionally in older but highly susceptible individuals. However, the regressive lesions such as encapsulated caseous and calcified tubercles in the pulmonary parenchyma and regional lymph nodes, and the slowly progressive lesions characterized by necrosis and cavitation, but accompanied by fibrosis and frequently associated with intracanalicular extensions, have been impossible to duplicate in laboratory animals with the exception of the dog. This animal possesses a high degree of natural resistance to tuberculosis but sometimes acquires the disease without experimental intervention because of its close association with man (1). The experiences of various investigators with spontaneous and experimental tuberculosis in dogs have been briefly reviewed in a previous publication (2).

The most successful method of inoculation from the standpoint of producing single lesions in the lungs is that of intrabronchial insufflation. This method was used by Lewis and Montgomery (3) in 1913 in a study of tuberculosis in dogs but Lamar and Meltzer (4) had used essentially the same technique in a study of experimental pneumococcal pneumonia at an earlier date. With various modifications this method of introducing a catheter directly into the bronchial lumen has been much used subsequently for introducing pathogenic bacteria and other foreign substances into the pulmonary parenchyma. We have found it most convenient to use a bronchoscope for the insertion of the catheter so that it could be introduced under direct vision into the orifice of a secondary bronchus. The placing of the infective inoculum is especially important when X-ray examination of the resulting lesions is to be made, for in the dog, as in the human subject, fairly large lesions may be obscured by the shadows of the heart and liver if they are unfavorably located.

In microscopical studies of primary lesions (2, 5) it was found that in the dog, infected by intrabronchial insufflation of 1.0 mg. to 10.0 mg. of virulent human or bovine type tubercle bacilli, the parenchymal lesion in its early stage is in the form of an exudative pneumonitis in which polymorphonuclear neutrophils at first predominate, accompanied by mononuclear leucocytes, mobilized septal

[1] From the Departments of Pathology, Bacteriology and Radiology, Northwestern University Medical School, Chicago, Illinois.

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cells and variable but usually small quantities of oedema fluid, fibrin and erythrocytes. Large mononuclear cells of the macrophagic type rapidly increase in number and size and usually dominate the field after two days. The lesions enlarge by direct extension, become more compact and centrally necrotic. Caseation may begin as early as two weeks after the injection. The size of the initial lesion, the extent of the necrosis and the final outcome of the process, whether regression with fibrosis and finally complete sterilization or progression to a fatal outcome, are determined to an important degree by the size of the infecting dose of tubercle bacilli.

The development of hypersensitivity to tuberculo-protein in infected dogs has been proved by the results of numerous intracutaneous tests (6) to occur within seven to twelve days, usually reaching a maximum within sixty days. The purpose of the experiments recorded here was to study in dogs any observable differences between the results of infection with virulent tubercle bacilli, introduced by the bronchial route into the pulmonary parenchyma, in previously infected animals as compared with those observed in animals infected for the first time.

MATERIALS AND METHODS

The dogs used in the experiments were largely mongrels, obtained from the pound with the exception of the puppies used in the second experiment which were born in the animal quarters of the laboratory. Males were used whenever obtainable and, as far as possible, the dogs to be used for controls were matched for size, general type and state of nutrition with their reinfected experimental mates. All dogs were isolated for at least one week before being used experimentally and observed for signs of acute respiratory infections, mange or other disease that would interfere with our observations. Some of the dogs used as controls in these experiments are identical with some of those previously described as subjects of primary infection.

Details of the technique used in preparation of the suspensions, introduction of the infective inoculum, intracutaneous tuberculin tests, X-ray examination and other procedures have been described in previous publications (2, 6). The cultures of tubercle bacilli and dosage are discussed in each of the three experiments.

HYPERSENSITIVITY FOLLOWING PULMONARY INFECTION WITH VIRULENT TUBERCLE BACILLI

The cultures of tubercle bacilli used for the primary inoculation of the lung were of the same virulent human strain (G2) as that used for the final dose. This strain has been maintained for several years in serial cultures on glycerolated egg-yolk medium and titrated from time to time for relative virulence in guinea pigs (7) and mice (8). A gradual diminution of virulence has been observed during the past few years but, since direct comparisons are made only between individual dogs that were injected at the same time from the same suspensions, this loss of virulence has led to no difficulty in interpretation of results. Thirty-two dogs were used in the first experiment. One-half of them were used as "primary" controls and the others were subjected to one or more sensitizing infections before receiving the final inoculation. In 9 dogs a 1.0 mg.

dose was used for the sensitizing inoculation, 0.33 mg. in one and 2.5 to 5.0 mg. in 6. The 6 dogs receiving the larger doses were among the first 50 dogs infected and it was not expected at the time that the initial mortality would be so great as it finally proved to be. Of 17 dogs which were inoculated at the same time with doses of 2.5 to 5.0 mg., 5 died of tuberculosis in forty-six to ninety days after inoculation. In a larger series of primary infections with similar doses the mortality was found to be about 30 per cent to 35 per cent and that in dogs infected with 1.0 mg. doses about 6 per cent. Therefore, 6 of the dogs in this experiment were assumed to possess a natural resistance to tuberculous infection superior to that of the average of dogs selected for experimentation from the stock. Since a similar selection of control dogs could not be made until after the termination of the experiment, it was to be expected that the mortality from tuberculosis in the controls would be greater than that of dogs surviving one or more previous infections resulting from similar doses of tubercle bacilli. Adjustments must therefore be made in comparing mortality figures.

Five of the reinfected dogs received a second intrabronchial injection before the final test doses were given with the expectation that the degree of hypersensitivity and immunity would be further increased.

After allowing a suitable interval (one hundred and sixteen to four hundred and twenty-eight days) for healing of the lesions which resulted from the preliminary injection or injections, the final infecting dose was introduced intrabronchially in the hypersensitive dogs and at the same time in an equal number of previously uninfected dogs. In 9 of the hypersensitive dogs the final dose was greater than the sensitizing dose and in 7 both doses were the same. The final doses varied from 1.0 mg. to 10.0 mg. In 12 pairs it was the same in hypersensitive and control dogs. In 5 pairs the dose was determined on the basis of body weight and was slightly greater in the previously infected than in the control dogs. Since those animals which had been previously inoculated had been under observation for periods up to twenty-one months, some had become heavier than the uninfected dogs more recently received from the pound. Consequently the controls available at the time were in some cases considerably lighter in weight and the total dose, calculated on the basis of 0.5 mg. per kilogram, were smaller for the controls than for their hypersensitive mates. These differences in dosage in the 5 pairs did not prove to be decisive in any manner, as will be shown later.

With the exception of one dog in which the results of tuberculin tests were not recorded, all of the dogs which received sensitizing injections had showed positive reactions at some time before the final inoculation. One was graded as 1 plus (Aronson's standard) and the rest were 2 plus to 4 plus when tested by intracutaneous injection of the standard dose (1.0 mg. of OT or 0.01 mg. of PPD). In 10 dogs the result of a test done a few days before the time of final inoculation was the same as that of maximal reactivity. In 3 there was a slight decline (1 plus) of reactivity and in one (no. 4) a decline from 2 plus to negative at the time of the last injection.

Six dogs of this group died, 3 of tuberculosis and 3 of other causes, within four days after inoculation. One of the latter was a reinfected dog, found dead

on the fourth day with a crushed liver and intraperitoneal haemorrhage. (Such accidents have occurred a few times when a dog unexpectedly jumped from a cage of the upper tier as the door was opened.) One died in two days and one in four days of acute bronchopneumonia. The 3 spontaneous deaths from tuberculosis were in dogs of the "primary" group and occurred at forty-eight, fifty-two and sixty-two days following inoculation with 3.0, 5.0 and 3.0 mg. of tubercle bacilli, respectively. In addition to the 6 dogs found dead, there were 2 that were killed with ether while apparently in a moribund state. One of these, reinfected dog no. 98, had a necrotic lesion of the right middle lobe with pleural perforation, effusion and pneumothorax when examined postmortem eighteen days after injection. There is a little doubt that it would have died within a day or two, if allowed to survive as long as possible, and should be considered as a spontaneous death from tuberculosis. Its control, no. 126, was found on its side, unable to stand and apparently having some respiratory difficulty, on the twenty-sixth day. At necropsy the tuberculous lesions were not extensive and were considered insufficient to account for the terminal state of the animal. Small cocci were found in large numbers in disseminated inflammatory lesions of the lungs and in the regional lymph nodes. The pleura was not involved. There was focal necrosis of the liver in addition to a few epithelioid cell tubercles. Both of these dogs are included with totals of deaths from tuberculosis in spite of the doubt in the case of the last.

Before any correction is made for the inclusion of 6 dogs that manifested exceptional ability to withstand infection resulting from the injection of large "sensitizing" doses of virulent bacilli, the mortality from tuberculosis in this group of 32 dogs stands as one death in reinfected dogs and 4 deaths in controls. If correction is made by excluding from consideration only those which survived primary infection with 2.5 to 5.0 mg. and their corresponding controls, there are 2 deaths from tuberculosis in control dogs and one in reinfected dogs. If correction is made by discounting the primary mortality of approximately 33 per cent in the controls of these same 6 pairs, the result is the same.

HYPERSENSITIVITY FOLLOWING BCG VACCINATION AND ENHANCED BY PULMONARY INFECTION WITH VIRULENT TUBERCLE BACILLI

The second group of reinfected animals consists of 6 hypersensitive dogs and 8 controls. In 4, sensitization was first attempted by feeding them large doses of BCG when they were four weeks old puppies. The oral "vaccination" by repeated feeding of living cultures of BCG (total dose about 350 mg.) was only partly successful. Before receiving the first inoculum containing virulent bacilli, one showed negative tuberculin reactions on two tests, 2 were 1 plus and one was 2 plus. The first intrabronchial injection was made one hundred and five days after the first day of BCG feeding and the dose used was 0.1 mg. per kg. (total doses: 0.37, 0.48, 0.46 and 0.5 mg.). In the other 2 dogs sensitization had been accomplished by intravenous injection of BCG and, after an interval of five months, each had been infected intrabronchially with 1.0 mg. of a virulent human strain.

The first dose of virulent bacilli was tolerated well by all 6 dogs. Dermal

tests indicated an enhanced reactivity to tuberculin in all, one of the puppies showing a 4 plus test and all of the others 2 plus. The puppies continued to gain weight up to the time of the second intrabronchial inoculation. Two control dogs, injected for the first time with doses of 1.0 mg. each, apparently tolerated their infection as well as any of the vaccinated dogs and, when sacrificed several months later, showed completely arrested lesions, one only a scar.

The final infective dose of 1.0 mg. each in the 2 older dogs was injected intrabronchially sixty-six days after the previous dose had been given and was intended to produce a superinfection lesion, arising during the period of maximal allergy. At the same time a similar dose was given to 2 previously uninfected dogs to serve as a second pair of controls for the 2 hypersensitive dogs. One of the latter (no. 59) and its control were sacrificed fourteen days after the final injection and examined for lesions. No. 55 and its second control were allowed to live for more than three and one-half years and, when examined, showed complete healing of all lesions.

The 4 dogs which were vaccinated as puppies and their controls received a final dose of 10.0 mg. of human strain intrabronchially about sixteen months after the small sensitizing dose had been given. The 3 males and their proper controls were killed with ether after periods of sixteen days, fifty-eight days and one hundred and seven days. The fourth pair were females and were allowed to live until they died. No. 100 had been pregnant repeatedly during the experimental period, each time giving birth to live puppies. Tuberculin tests had been positive early and reached a maximum of 2 plus about three months after the BCG feedings. Dermal reactivity remained high and was increased by infection with virulent bacilli, occasionally giving a 4 plus reaction (central necrosis in a large wheal). After a rapid loss of weight during a period of three or four weeks, death occurred from extensive pulmonary tuberculosis with empyema and numerous lesions in the abdominal viscera, five hundred and forty-five days after the administration of the test dose. The control died of pyogenic uterine infection and general sepsis, developing during pregnancy, two hundred and fifty-three days after injection. The tuberculous lesions were completely healed and represented by scars of parenchyma and pleura with pleural adhesions and small scars in the tracheobronchial lymph nodes.

No consistent differences either in the pulmonary lesions or in the degree of involvement of the lymph nodes were observed in this small group of reinfected dogs, as compared with their controls which were infected only once. The death from tuberculosis of one animal from a group of 8 can have no statistical significance in an experiment of this kind. For purposes of comparison of the lesions of reinfection with those of first infection at various periods of development this group of dogs is combined with the other two groups, one of which has been described, and listed in tables 1 and 2 in the order of the age of the most recent infection of the reinfected dogs.

HYPERSENSITIVITY FOLLOWING INTRATESTICULAR INOCULATION

In this experiment, sensitization was accomplished by the injection of measured doses of virulent tubercle bacilli into the testes of 10 dogs. In 7 dogs, 1.0

mg. doses and in one dog a 5.0 mg. dose of human type bacilli (G2), suspended in sterile salt solution, were used. The interval between the time of intratesticular injection and of intrabronchial inoculation in the first 8 dogs was from two hundred and sixty to eight hundred and forty days. For the intrabronchial inoculation, mucinous suspensions of four weeks old cultures of bovine type bacilli (Ravenel) were used, since the human type strain used in most of the previous experiments had begun to show a decline in virulence. The dose was 1.0 mg. in 8 dogs, including the controls, and 10.0 mg. in 8. In 2 dogs the testis was injected with 15.0 mg. doses of a somewhat attenuated bovine strain of tubercle bacilli and, after an interval of seventy-three days, intrabronchial inoculations with 1.0 mg. doses of human type (G2) bacilli were made. These 2 with their controls, inoculated intrabronchially at the same time and with the same dose, were sacrificed after seven days and fourteen days for the purpose of comparing the relative size and histological structure of their lesions.

The control dogs were selected at the same time as were those for intratesticular injection and matched as closely as possible for weight, general build and state of nutrition. At the beginning of the experimental period each dog to be sensitized and its control weighed within 2 or 3 kg. of each other. At the time of intrabronchial inoculation a few marked discrepancies in weight had occurred. Dog no. 77 which had received 5.0 mg. of human type bacilli gained 7 kg. in the eight hundred and forty day interval and weighed 21 kg. at the time of intrabronchial inoculation. Two of the control dogs weighed approximately 17 kg. each at the time of injection and outweighed their hypersensitive mates by 7 kg. and 8 kg., respectively. However, at the time of intrabronchial injection, the average weight of the 10 hypersensitive dogs was 11.31 kg. and the average of the controls was 11.46 kg. Each hypersensitive dog and its control were injected at the same time and with the same dose regardless of body weight.

In this group, the term "hypersensitive" should be used with reservations, since 3 of those sustaining testicular infections showed negative tuberculin tests made with 0.1 cc. of 0.01 per cent solution of PPD a few days before the intrabronchial inoculation was made. Five showed 2 plus to 3 plus reactions and 2 were recorded merely as "positive." Tuberculin tests in all of the 10 controls were negative. Two of the 3 dogs that gave negative tests before the pulmonary infection showed at necropsy active granulomatous lesions of the injected right testis. The third showed extensive scarring and atrophy of the injected testis. The success of the intratesticular injection was verified in every case by repeated examination of the testis during the period of swelling and induration, followed later by atrophy.

Spontaneous deaths were more numerous in the hypersensitive dogs than in the controls. Three of the 4 reinfected dogs that had been inoculated with 10.0 mg. doses of bovine type bacilli died of extensive pulmonary tuberculosis at the end of twenty-eight, sixty-nine and eighty-two days and one of the 4 which had been inoculated with 1.0 mg. died after two hundred and sixty-six days with generalized visceral tuberculosis as well as active pulmonary lesions. Two died of disease other than tuberculosis in three hundred and twenty-eight days and six hundred and twenty-seven days after the time of intrabronchial

injection. Two of the control dogs died in three hundred and fourteen and three hundred and twenty-eight days after injection with 10.0 mg. doses of bovine type bacilli. In one of the latter the pulmonary lesions consisted of a completely healed primary focus and scattered miliary tubercles in all lobes. There were small but active granulomatous lesions in the liver and one kidney. There was some doubt that tuberculosis was the cause of death in this case but it is included in the statistical analysis as a tuberculous death. In the other, the pulmonary lesion was an encapsulated caseous nodule in the right middle (cardiac) lobe and there were no recognizable lesions elsewhere. The cause of death was undetermined.

COMPARISON OF LESIONS IN REINFECTED AND CONTROL DOGS

In the 32 reinfected dogs of the three groups, the strain of tubercle bacilli used for sensitization was the same for all, except the 2 which received an intratesticular injection of bovine type bacilli. The previous sensitization of 6 dogs with BCG should make little difference in the results, except to enhance the degree of allergy later developed as a result of pulmonary infection with virulent human type tubercle bacilli. The evidence of repeated tuberculin tests supports this view. The infective inoculum responsible for the final infection contained various doses of human type cultures in 24 reinfected dogs and their controls and doses of 1.0 mg. or 10.0 mg. of virulent bovine type bacilli were used for the test inoculation in 8 reinfected dogs and their controls. No outstanding difference between these two strains in their virulence for dogs was observed in the earlier experiments but during the later part of the period the human type strain gave evidence of decline of virulence.

For purposes of comparing the extent and composition of the tuberculous lesions in dogs previously hypersensitive to tuberculin with those which were normal previous to inoculation with the test dose, the three groups are combined in tables 1 and 2 in which they are arranged, each opposite its own control, in the order of the age of the pulmonary infection resulting from the most recent inoculation. Since profitable comparisons cannot be made between dogs that have died spontaneously from progressive tuberculosis, these with their proper experimental mates are not included in the tabulation. The comparison is made in respect to the types of lesions found in the injected lobe, the diameters of the principal lesions and the presence and extent of caseous necrosis and cavity formation. In estimating the relative values for cavitation, the volume of a single cavity, or of the aggregate if multiple, was roughly estimated from the diameters and the result expressed in plus signs. Caseation was verified by microscopical sections made through the lesions at different levels. We have found that a false impression of the extent of caseation may be obtained from macroscopical inspection alone, since simple coagulative necrosis can be mistaken for true caseation, especially in formalin-fixed tissues. In table 2 the comparative degrees of hypertrophy, epithelioid cell hyperplasia and caseation of the tracheobronchial lymph nodes and the presence and extent of tuberculous lesions in the kidneys, liver and spleen are indicated by plus signs. The com-

parative degrees of hypertrophy of lymph nodes were estimated by calculating the volume from the diameters of the largest single node or fused mass of nodes and the results expressed in plus signs in the table. An increase in volume over the average normal of two to five times is indicated as 1 plus; five to ten times as 2 plus; ten to twenty times as 3 plus and over twenty times as 4 plus. Estimates of degrees of hyperplasia are based upon the extent of replacement of normal parenchyma by epithelioid cells in microscopical sections of the larger nodes, complete replacement being expressed as 4 plus in the table.

Two to five days: In periods less than one week the lesions of hypersensitive and control dogs are not strictly comparable since one of the control dogs died after two days of acute "distemper" bronchopneumonia and one of the reinfected dogs died of trauma after four days, while their experimental mates were killed with ether on the fourth and fifth days, respectively. No. 64 sustained a four day lesion which was much larger than that of its control which was of only two days development. Similarly the diameter of the five day old primary lesion of no. 151 was larger than the reinfection lesion of its experimental mate, no. 108, dead at four days. Dog no. 108 showed evidence of scattering of the infectious exudate in the form of small peribronchiolar lesions in all lobes. The largest single tracheobronchial lymph node of the control (no. 151) was slightly larger than that of 108 and showed also a greater degree of hyperplasia of reticulum cells.

Seven days: In the next 3 pairs, killed with ether at the end of a week, more satisfactory comparisons can be made. The largest principal pulmonary lesion was found in reinfected dog no. 8; its control had a much smaller lesion at necropsy, although it had received the same dose (5.0 mg.). The next largest lesion was found in control dog no. 92; that of its experimental mate was much smaller. In dog no. 41 and its control no. 94 the diameters of the pulmonary lesions were more nearly the same. The degree of hypertrophy, hyperplasia and epithelioid cell transformation (discrete and confluent tubercles) of the lymph nodes was greater in the three control dogs. No necrosis was present in any of the lesions of these 6 dogs.

Fourteen and sixteen days: In 6 dogs sacrificed at the end of two weeks and 2 at sixteen days, the lesions showed individual differences but no group differences in size or composition. A slight scattering of the inoculum in no. 76 (control) and in no. 89 (reinfected) had resulted in the formation of a central solid mass and numerous satellite lesions in the same lobe so that the diameters are not comparable. In the 4 pairs, the reinfected lesions were larger in 2 and the primary lesions were larger in the other 2. Caseation was evident in 2 of the 4 reinfection lesions (1 plus and 2 plus) and in 3 of the primary lesions (1 plus each). The lymph nodes of 2 of the reinfected dogs (nos. 16 and 101) were larger than those of their respective controls, those of the control were larger in one pair and they were nearly of the same size in one pair. Caseation was present in one or more lymph nodes in no. 16 (reinfected) and in no. 96 (control). These were the 2 of the group that had the largest pulmonary lesions and the greatest degree of hypertrophy and epithelioid cell hyperplasia of the lymph

TABLE 1

REINFECTION							PRIMARY						
Dog number	Survival	Principal lesion					Dog number	Survival	Principal lesion				
		Site	Form	Diameter	Caseation	Cavitation			Site	Form	Diameter	Caseation	Cavitation
	days			*mm.*				*days*			*mm.*		
64	4	RUL	Solid exudative	50 x 30 x 15			112	2*	RML	Confluent bronchopneumonic	25 x 20 x 10		
108	4*	RML	Solid exudative and proliferative	45 x 30 x 20			151	5	RUL	Solid exudative and proliferative	50 x 40 x 22		
8	7	RLL	Solid exudative and proliferative	70 x 70 x 25			124	7	RUL	Confluent bronchopneumonic	30 x 25 x 15		
41	7	RLL	Solid exudative and proliferative	40 x 40 x 20			94	7	RML	Solid exudative and proliferative	45 x 30 x 20		
90	7	LLL	Solid exudative and proliferative	25 x 25 x 20			92	7	LLL	Confluent bronchopneumonic	45 x 30 x 30		
16	14	LLL	Confluent bronchopneumonic	70 x 65 x 30	+		76	14	LLL	Solid granular pneumonia	25 x 20 x 13	+	
89	14	RLL	Solid granulomatous pneumonia	30 x 25 x 20			91	14	RLL	Solid granulomatous pneumonia	45 x 45 x 30		
59	14	Int.	Solid granulomatous pneumonia	30 x 25 x 23	(Coagulative necrosis)		96	14	RLL	Solid granulomatous pneumonia	80 x 60 x 25	+	
101	16	RLL	Solid granulomatous pneumonia	65 x 35 x 35	++		150	16	RUL	Solid granulomatous pneumonia	50 x 50 x 25	+	

73	27	LML	Solid granuloma	50 x 40 x 30	+		131	27	LML	Solid granuloma	45 x 40 x 25	(coagulative necrosis)	+
82	46	LML	Granuloma; cavities	40 x 30 x 30	++	++	130	46	LML	Granuloma; cavities	45 x 35 x 35	(coagulative necrosis)	++++
103	58	RUL	Confluent granlomatous bronchopneumonic	55 x 35 x 25	(coagulative necrosis)	+++	153	58	RUL	Granuloma; cavity	36 x 32 x 30	+	+++
5	92	RLL	Granuloma; cavity	50 x 40 x 35	(coagulative necrosis)	+++	33	93	RLL	Healed cavity	15 x 12 x 12		++
77	96	RLL	Healed cavity	12 x 8 x 8		++	202	96	RLL	Granuloma; cavity	12 x 10 x 8	(coagulative necrosis)	++
102	107	RLL	Healed cavity	18 x 14 x 8		++	152	107	RML	Scar			
174	138	RML	Scar				198	138	RML	Encapsulated Nodule	15 x 14 x 10	++	
49	210	LML	Healed cavity	15		++	129	210	LML	Scar			
4	215	RLL	Encapsulated nodule	13	+++		42	215	RLL	Scar			
47	245	RLL	Healed cavity	30 x 15 x 15		++	128	223	RML	2 encapsulated nodules	27 x 17 x 16	+++	
179	328*	RML	Scar				204	517	RUL	Encapsulated nodule	18 x 12 x 10	++	
176	627*		No lesion				199	630	RUL	Scar			
55	1,354	RUL	Scar				97	1,306	RML	Scar			

* Died spontaneously from nontuberculous causes.

RUL = right upper (apical) lobe. RML = right middle (cardiac) lobe. RLL = right lower (major or diaphragmatic) lobe. LUL, LML, LLL = left upper, middle and lower lobes. Int. = intermediate lobe (medial fourth lobe of the right lung).

TABLE 2

REINFECTION								PRIMARY							
Dog number	Survival	Lymph nodes			Hematogenous tuberculosis			Dog number	Survival	Lymph nodes			Hematogenous tuberculosis		
		Hypertrophy	Hyperplasia	Case-ation	Kidney	Liver	Spleen			Hypertrophy	Hyperplasia	Case-ation	Kidney	Liver	Spleen
	days								*days*						
64	4		±†					112	2*		±				
108	4*	++	±					151	5	++	±				
8	7	++	++					124	7	++	+++			+	+
41	7	+				+		94	7	++	++				
90	7	++	++					92	7	+++	++				
16	14	++++	++++	+	+	++		76	14	+++	++		+	++	+
89	14	++	++					91	14	++	++				
59	14	+	+			+		96	14	+++	+++	++		+	
101	16	++++	+++			+		150	16	++	+++			+	
73	27	++	+			+	+	131	27	++++	++++	+	+	++	+
82	46	+	++			+		130	46	++++	++++	+		++	
103	58	+++	+++			+		153	58	++	++			+	
5	92	++	++					33	93		+				
77	96		+		+++	+		202	96	+++	+++				
102	107							152	107						
174	138					+		198	138		+		+	++	
49	210	+++	++		++	+		129	210						
4	215	+	±					42	215						
47	245	+						128	223	++	+			+	+
179	328*							204	517						
176	627*							199	630						
55	1,354							97	1,306	+					

† The symbol ± indicates instances of reticulum cell hyperplasia but absence of definite epithelioid cell transformation.

nodes. Six of these dogs showed epithelioid cell tubercles in the liver, no. 16 (reinfected) and no. 76 (control) showing more extensive hepatic lesions. The same 2 had tubercles in the kidneys and one (no. 76) had tubercles in the spleen.

Twenty-seven days: Three dogs were killed with ether twenty-seven days after the final inoculation. One of the 2 controls (no. 99) had died of acute haemorrhagic bronchopneumonia four days after injection. In reinfected dog no. 63 there were multiple solid nodules up to 2 cm. in diameter, composed chiefly of histiocytes and macrophages, and there was no evidence of necrosis. The nodes were diffusely hyperplastic but showed no definite tubercles. In dog no. 73 and its control no. 131 the pneumonic lesions were nearly equal in size and a small quantity of pleural fluid was present in each at necropsy but the degree of involvement of the lymph nodes was much greater in the control. Early caseation (1 plus) was present in the pulmonary lesion of the reinfected dog. In the control there was no caseation but the disintegration of small areas of coagulative necrosis had resulted in very early cavity formation. Caseation was present in the lymph nodes of the control dog but none in its reinfected mate. Haematogenous lesions were more widely distributed and more numerous in the former.

Forty-six days: In the 2 dogs examined at the end of forty-six days, each having received 5.0 mg. of human type bacilli, the pulmonary lesions did not differ significantly in size. Necrosis and cavitation were greater in the control but true caseation was present only in the lung of the reinfected dog. Intrabronchial extensions in the same lung as the principal lesion was present in both. Hypertrophy and hyperplasia of lymph nodes were greater in the control and coagulative necrosis with minimal caseation was present in its larger nodes. Epithelioid cell tubercles were present in the livers of both.

Forty-eight days: The pulmonary lesions in these 2 dogs were the result of infection with 10.0 mg. doses of human type bacilli. The larger was found in the reinfected dog. The lesions of both were excavated. Partial encapsulation was evident in microscopical sections of the lesion of the primary infection. The degree of involvement of the lymph nodes was greater in the reinfected dog. There were epithelioid cell tubercles in the liver of each.

(The 6 dogs discussed in the following three paragraphs are not included in the tables, since one member of each pair died spontaneously of tuberculosis. In 2 pairs the wide difference in age of the lesions resulting from the test inoculation would of itself preclude profitable comparisons.)

The control dog no. 127 died after sixty-two days following perforation of a necrotic lesion into the pleural cavity with granulomatous pleuritis, mediastinitis and pleural effusion. Bronchiolar pneumonia was present in all lobes. The lymph nodes while not so large as those of its reinfected mate showed more advanced caseation. The reinfected dog, sacrificed at sixty-five days, had a relatively large pulmonary lesion with multilocular thick-walled cavities and small areas of caseation in their walls. The lymph nodes were hyperplastic but not caseous.

Of the next pair, the reinfected dog died after sixty-nine days with a perforated

caseous pulmonary lesion, pleural effusion, pneumothorax and bronchiolar lesions of both lower (major) lobes. The control dog lived three hundred and twenty-eight days after inoculation and did not die of tuberculosis. Its pulmonary lesion was an encapsulated caseous node in the right middle lobe. The lymph nodes were not appreciably enlarged and contained only a few minute nests of epithelioid cells. The difference in outcome in these 2 may perhaps be accounted for on the basis of the accident of perforation of the pleura.

Such an explanation would certainly not suffice in the case of the next pair of which the reinfected dog (no. 175) died eighty-two days after intrabronchial inoculation of 10.0 mg. of bovine type tubercle bacilli. Death was caused in this dog by extensive tuberculous bronchopneumonia, following intrabronchial evacuation of a necrotic granulomatous lesion of the right middle lobe. Its control (no. 203) was sacrificed after five hundred and seventeen days. Its primary lesion was healed and represented by a thin-walled cyst-like cavity. The nodes showed only slight scarring and no active lesions. There was a small granulomatous lesion in one kidney in which a few acid-fast bacilli were found.

Ninety-two and ninety-six days: In these 2 pairs the dose was 1.0 mg.; in one a human type strain and in the other, bovine. All were in good condition when they were scarificed for study. Dog no. 5 with a 2 plus tuberculin test at the time of reinjection showed the largest lesion of the 4 at the time of necropsy. The centre of the lesion had broken down to form multilocular cavities. The pulmonary lesion of its control (no. 33) was completely evacuated and healed but there were many small peribronchiolar exudative lesions in all lobes. The cellular composition and the presence of acid-fast bacilli proved that these were tuberculous. The lymph nodes were only slightly enlarged and hyperplastic and contained a few small foci of epithelioid cells. Dog no. 77, also showing a 2 plus dermal test, had been sensitized by intratesticular infection. Its pulmonary lesions resembled those of control no. 33 and consisted of an obsolete fibrous-walled cavity and a few small widely disseminated lesions of recent origin. Both kidneys and liver contained active tuberculous lesions. No. 202, the proper control for no. 77, had as its primary lesion a small cavity, surrounded by a wall of granulation tissue. The nodes were diffusely hyperplastic and showed minimal coagulative necrosis but no true caseation. There were no haematogenous foci in this case.

One hundred and seven days: The lesions of both control and reinfected dog at this period were completely healed. A completely fibrous, thin-walled cavity marked the site of the reinfection lesion in dog no. 102 and the lymph nodes were essentially normal. The primary lesion of no. 152 consisted of a pigmented (carbon) scar of the parenchyma and fibrous thickening of the pleura. Calcareous granules were found in the lesions of both dogs by microscopical examination.

One hundred and thirty-eight days: Dogs no. 174 and no. 198 had each received 1.0 mg. of bovine type bacilli in the right middle lobe. Both survived in good condition and were killed with ether at the end of one hundred and thirty-eight days. The pulmonary lesions of both were confined to the site of injection. In

the reinfected dog (no. 174) there was only a fibrous pleural and parenchymal scar. The lymph nodes were normal. In the control dog the lesion was a small encapsulated, partly caseous granuloma, surrounded by a few small compact granulomatous nodules. The lymph nodes contained a few minute epithelioid cell tubercles. Haematogenous foci were found in both but they were more numerous in the control dog. The testicular primary lesion in no. 174 was entirely inactive and fibrous.

Two hundred and ten to two hundred and sixty-six days: Eight of this group of 10 dogs received doses of human type bacilli ranging from 5.0 mg. to 8.0 mg. (0.5 mg. per kilogram of body weight) and 2 received 1.0 mg. each of bovine type culture. One control (no. 75) of the group died at the end of fifty-two days with extensive tuberculous broncho-pneumonia, bilateral pleural effusion and granulomatous infiltration of the mediastinum. One of the reinfected dogs (no. 161) died of tuberculosis two hundred and sixty-six days after intrabronchial insufflation of 1.0 mg. of bovine type culture. Its pulmonary lesions consisted of a partly healed cavity and an unencapsulated granuloma in the right lower lobe just outside of the cavity. The bronchial nodes were only slightly hyperplastic. The only caseous lesion was a granuloma of the wall of the aorta and this was presumably the source of the numerous haematogenous visceral lesions. (These 2 dogs with their experimental mates are not included in the tables.) The other 8 dogs were apparently in good condition when sacrificed for examination. The pulmonary lesions of 2 of the 5 controls at the end of two hundred and ten and two hundred and fifteen days were represented by scars only and the tracheobronchial nodes were normal. One (no. 128) showed two partly encapsulated granulomatous nodules, about 75 per cent caseous and infiltrated with lime salts. The nodes in this animal were enlarged, hyperplastic and contained epithelioid cell tubercles. The fifth had a completely obsolete, fibrous-walled cavity (5 mm. in diameter) and pleural scars. In 3 of the reinfected dogs the pulmonary lesions were healed, one (in no. 48) with a scar only and 2 (nos. 49 and 47) with healed thin-walled cavities. One of the latter, however, showed marked hypertrophy and epithelioid cell hyperplasia of the tracheobronchial lymph nodes, granulomatous pericarditis, tuberculous pyelonephritis and epithelioid cell tubercles in the liver. In the fifth reinfected dog of the group (no. 4) the pulmonary lesion was an encapsulated caseous and slightly chalky nodule in the right lower lobe and the lymph nodes contained only fibrous scars.

Three hundred and twenty-eight to one thousand three hundred and fifty-four days: With the exception of one pair, precise comparisons are not possible in the last 10 dogs (6 included in the tables) since 5 of them died, 3 reinfected dogs and 2 controls. In 2 of the 3 reinfected dogs that died at the end of three hundred and twenty-eight and six hundred and twenty-seven days respectively no active lesions were found in the lungs or elsewhere. In the latter case not even a pleural scar was found and it must be concluded either that the lung was not successfully injected or that the lesion had been centrally located, not involving the pleura, and had completely resolved. Following intratesticular

inoculation this dog had shown a 3 plus cutaneous reaction to tuberculin. This degree of sensitivity had been maintained until the time of intrabronchial inoculation with 1.0 mg. of bovine type bacilli and was not appreciably increased afterward. A single X-ray film made eighty-four days after the test inoculation showed no definite evidence of a pulmonary lesion. In the third dog that died (no. 100) death occurred after five hundred and forty-five days from extensive tuberculous bronchopneumonia and empyema. Reinfected dog no. 95 survived and gained weight after being subjected to a final intrabronchial injection of 3.5 mg. of human strain bacilli. At necropsy three and one-half years later both the primary lesion in the left lower lobe and the reinfection lesion in the right lower lobe were completely cicatrized but a seminecrotic, slightly caseous granuloma of the first part of the aorta was evidently still active and had given rise to microscopical epithelioid cell tubercles in the mediastinal lymph nodes and in the liver. These were the only active lesions found. In the fifth reinfected dog (no. 55), sacrificed to terminate the experiment after one thousand three hundred and fifty-four days, the only lesions were scars in the lung and lymph nodes.

Among the proper controls of these 5 dogs there was one early death from tuberculosis (forty-eight days in dog no. 125). The primary lesions of the remaining 4 (nos. 204, 154, 199 and 97) and 4 other control dogs (nos. 201, 203, 205 and 209, not included in the table) which were examined after experimental periods greater than three hundred days from the time of infection, were effectively arrested and encapsulated (204 and 209) or completely cicatrized but in 2 dogs with obsolete primary lesions (205 and 203) there were active tuberculous lesions in the kidneys after three hundred and fourteen and five hundred and seventeen day periods respectively. The diameters of the tracheobronchial lymph nodes were within normal limits or very slightly enlarged (no. 97) in all of these 8 dogs but small foci of epithelioid cells were found in 2 of them (nos. 205 and 209) at three hundred and fourteen and three hundred and twenty-eight days. No active lesions were found in any of the 3 control dogs which were sacrificed after a period of more than six hundred days.

DISCUSSION

A detailed statistical comparison of mortality figures in 64 dogs of uncertain antecedents and various ages would be unprofitable since the differences are relatively slight, especially when viewed as a single experiment. A preliminary analysis of the mortality data brings out two factors which appear to influence the outcome, namely the size of the dose and the location of the principal lesion. Unfortunately the relative importance of these two factors cannot be determined in this series since they are operative in the same experimental animals. In the entire series there were 11 dogs in which spontaneous death was attributable to tuberculosis, 6 in dogs which were reinfected and 5 in controls. In only one of these was the dose of tubercle bacilli less than 3.0 mg. Of the 8 dogs receiving 10.0 mg. of bovine type bacilli, 4 died of tuberculosis. Of 24 receiving 3.0 mg. to 10.0 mg. of human strain bacilli, 6 died and, of the 14 (those sacrificed within

three weeks are not considered) injected with 1.0 mg. doses of human bovine type bacilli, only one died.

Upon first survey the site of injection appears to be a determining factor in the outcome, since 7 of the 11 dogs that died of tuberculosis had their principal lesion in the right middle (cardiac) lobe and one in the left middle lobe. The upper (apical) and middle lobes are much smaller than the lower (major) lobes in the dog's lung and the inflammatory lesion quickly reaches the pleural surfaces, frequently involving the entire lobe in the case of the middle lobes. Seven of the 11 tuberculous deaths were associated with pleural effusion and 6 of these were due to pleural involvement from lesions in the middle lobes. To conclude that this relationship was a determining factor, however, would be fallacious since we do not have an equal number of dogs injected with equally large doses of tubercle bacilli in other lobes with which to make comparisons. The fact that none of the 14 dogs died after being injected with 1.0 mg. doses in one of the minor lobes (apical or cardiac), however, suggests that the size of the dose and not the site of the lesion is the more important factor. Approximately one-half of the total number of dogs, not including those sacrificed within the first three weeks, were inoculated in one of the minor lobes but these included a disproportionately large number of those receiving the largest infecting doses of tubercle bacilli.

The influence of acquired immunity and sensitization upon mortality or survival time is not decisive in these experiments. The gross spontaneous mortality in reinfected dogs was 9 and in controls 9. Deaths attributable to tuberculosis were 6 in reinfected dogs and 5 in controls, including one in each group which was sacrificed while moribund eighteen and twenty-four days respectively after infection. When correction is made for loading in favor of the reinfected dogs in the first experiment by eliminating the 6 reinfected dogs which survived pulmonary infection with the larger (2.5 to 5.0 mg.) doses and their controls, deaths from tuberculosis were 6 among the previously injected dogs (one in the first experiment, one in the second and 4 in the third) and 3 among the controls (2 in the first experiment and one in the third). Comparison of the duration of life in the dogs which succumbed to tuberculosis shows no significant difference between controls and their experimental mates whether comparisons are made between individuals or by making averages.

The question of protection has not been conclusively answered but points to the decision that acquired immunity is so slight that it is entirely obscured by the more decisive factors of individual susceptibility and size of the infecting dose. In order to estimate quantitatively such small degrees of acquired immunity, animals which are much more homogeneous than these in heredity and age would be necessary.

Regarding the question of the influence of hypersensitivity upon the type and extent of the pulmonary lesions, the results are more clear. It had been suspected that, if hypersensitivity and acquired specific immunity had any appreciable effect upon the development of the pulmonary lesion, that effect would be manifest within the first few weeks and that the differences, if any, between

lesions in animals previously infected and in those which had not been infected previously would tend to disappear as the latter also became hypersensitive. Hypersensitivity as indicated by the results of intracutaneous injection of tuberculin is evident usually in seven to twelve days and reaches a maximum within two months in at least two-thirds of infected dogs. The rest show a progressive increase of sensitivity up to five or six months, sometimes reaching a maximum of 3 plus or 4 plus. It had not been anticipated that reinfection lesions of less than two months' development would so closely resemble those of primary infection. The only indications of differences in size of the pulmonary lesions can be satisfactorily explained as individual differences since they are not predominantly in favor of reinfected dogs of their controls. In some of the former (nos. 8, 16, 103 and 5) the pneumonic lesion in each was larger than that of its proper control. In some of the controls (nos. 92, 91 and 96) the principal lesion was larger than that of its reinfected mate. In the rest of those dogs which were sacrificed within one hundred days of the time of the final injection, the pulmonary lesions were approximately equal in size in each pair of dogs. Caseation and cavity formation were not significantly more frequent or more extensive in one experimental group or the other.

The degree of involvement of lymph nodes in the tracheobronchial group as appraised on the basis of the diameters of the largest single node or fused mass of nodes and of the extent of epithelioid cell hyperplasia was, in general, slightly greater in controls than in reinfected dogs but the differences were quite irregular. The larger nodes were found in reinfected dogs almost as often as in the controls within the first one hundred days and after this period there were no appreciable differences. The largest group of tracheobronchial nodes found in any dog was seen in control dog no. 131, sacrificed twenty-seven days after inoculation with 5.0 mg. of human type tubercle bacilli. In the entire number of dogs there were only 8 in which true caseation was found in the lymph nodes. Three of these were reinfected dogs and 5 were controls. Four of the 8 died of tuberculosis. In members of both of the two major groups the degree of hypertrophy and extent of caseous necrosis of lymph nodes are clearly related to the extent and severity of the tuberculous process in the lungs and pleura. Haematogenous foci in liver, kidneys and spleen were common and about equally frequent in reinfected and control dogs.

SUMMARY

Hypersensitivity to tuberculoprotein as indicated by intracutaneous tests with Old Tuberculin or purified protein derivative (PPD) appears in the majority of dogs within a few weeks after intrabronchial or intratesticular injection of virulent tubercle bacilli. The maximum of cutaneous allergy is reached within a few months, most commonly within sixty days. When the first dose of human or bovine type bacilli is relatively small (1.0 mg. or less) the primary lesion usually heals completely with cicatrization, but hypersensitivity persists for a year or longer after healing is complete. Reinfection with an equal or larger dose of virulent bacilli, introduced intrabronchially after an interval of three to

twelve months from the time of first infection, results in the development of a pulmonary lesion which does not differ significantly in size, composition or ultimate outcome from a lesion resulting from injection of a similar dose in a previously uninfected dog, that is, there is no morphological evidence of a "primary type" and "reinfection type" of tuberculous lesions in adult dogs. The results of such infection upon tracheobronchial lymph nodes are the same or slightly more extensive in primarily infected than in previously sensitized dogs within a period of about two months after inoculation. After this period all differences tend to disappear. Caseation, calcification, cavity formation and fibrosis do not differ appreciably in the pulmonary lesions of primary infection from those of reinfection, but there is a greater tendency for caseation to occur in the regional lymph nodes of the primary complex. The results of these experiments indicate that resistance to tuberculous infection of the lungs of dogs is neither enhanced nor diminished in an important degree by the state of allergy (used in the broad sense) which results from a previous infection with virulent tubercle bacilli when the infective inoculum is introduced by the bronchial route. Differences in natural (inherited) resistance to tuberculosis and differences in size of dose appear to influence the results to an important degree but,under the conditions of these experiments, the effects of acquired specific immunity and hypersensitivity are comparatively insignificant.

SUMARIO

A las pocas semanas de inyectar por vía intrabronquial o intratesticular bacilos tuberculosos virulentos, los perros presentaron hipersensibilidad a la tuberculoproteína, según indica el resultado de las intracutirreacciones con tuberculina antigua o derivado proteínico purificado (PPD). La alergia cutánea máxima sobreviene a los pocos meses y más a menudo dentro de 60 días. Cuando la primera dosis de los bacilos de tipo humano o bovino es relativamente pequeña (1.0 mg o menos), la lesión primaria suele cicatrizar completamente, aunque la hipersensibilidad continúa por un año o más después de completarse la curación. La reinfección producida con una dosis igual o mayor de bacilos virulentos introducidos en los bronquios, al cabo de un intervalo de 3 o 12 meses desde la primera infección, produce una lesión pulmonar que no se diferencia significativamente en tamaño, composición o resultado final, de la lesión producida por la inyección de una dosis semejante en un perro previamente no infectado, es decir, que en los perros adultos no se observan signos morfológicos de lesiones tuberculosas de tipo "primario" y de "reinfección". El resultado de esa infección en los ganglios linfáticos tráqueobronquiales viene a ser idéntico o ligeramente más intenso en los perros con infección primaria que en los perros previamente sensibilizados en un período de unos dos meses después de la inoculación. Al cabo de ese período todas las diferencias tienden a desaparecer. La caseación, la calcificación, la formación de cavernas y la fibrosis no se diferencian apreciablemente de las lesiones pulmonares producidas por la reinfección, pero existe mayor tendencia a la caseación en los ganglios linfáticos regionales del complejo primario. El resultado de esos experimentos indica que la resistencia a la

infección tuberculosa en el pulmón de los perros no es aumentada ni disminuída mayor cosa por el estado de alergia (interpretado en un concepto amplio), que proviene de una infección previa con bacilos tuberculosos virulentos cuando el inóculo infectante es introducido por vía bronquial. En cambio las diferencias en la resistencia natural (heredada) a la tuberculosis y en la dosis parecen afectar en forma importante el resultado, pero en las condiciones de estos experimentos son comparativamente insignificantes los efectos de la inmunidad específica adquirida y de la hipersensibilidad.

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NEW DERIVATIVES OF DIAMINODIPHENYLSULFONE[1,2]

Their Therapeutic Effect in Experimental Tuberculosis of Guinea Pigs

FRITZ F. T. CALLOMON

With the technical assistance of Loraine Groskin

After the first reports of Rich and Follis (15, 16) on the inhibitory effect of sulfanilamide in experimental tuberculosis of guinea pigs, two opposing opinions developed concerning this effectiveness:

(*1*) That of the group of investigators who used exactly the same techniques as Rich and Follis and attained similar results, especially with sulfanilamide and sulfapyridine (Buttle and Parish (3); Greey, Campbell and Culley (10); Ballon and Gueron (1); Feldman and Hinshaw (6); Birkhaug (2)).

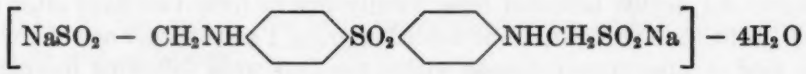
(*2*) That of the group of investigators who chose other routes of administration and also other sulfonamide derivatives and found comparative ineffectiveness of the drugs tested (Smithburn (18); Kolmer, Raiziss and Rule (13); Levin (14); Dietrich (5); Corper, Cohn and Bower (4)).

Striking results have been attained by Feldman and Hinshaw (8, 10) and their co-workers, however, in experimental tuberculosis of guinea pigs treated with the new diaminodiphenylsulfone compound promin. With the technique and dosage used in their experiments, promin produced evident inhibition of the spread and advancement of the disease. Furthermore, these investigators found during the period of observation of their animals, significant alterations in the histological structure of the lesions in the treated animals as compared with the untreated controls.

FIRST EXPERIMENT

In our first experiment we tried to compare the effectiveness of the usual sulfonamide compounds, that is, sulfanilamide, sulfapyridine, sulfathiazole and, in addition, sulfathiazoline (as yet not tested in experimental tuberculosis), with that of three diaminodisulfone derivatives, one of which was promin. The two new derivatives tested were compounds No. 2398 and No. 2816 obtained, as was sulfathiazoline, through the kindness of Dr. George W. Raiziss of the Dermatological Research Laboratories in Philadelphia (Division of the Abbott Laboratories, North Chicago, Illinois). We are indebted also to Dr. E. A. Sharp, Director of the Department of Animal Investigation, Parke, Davis & Co., Detroit, Michigan, for supplying us with the necessary amount of promin.

The structural formula of compound No. 2398 is as follows:

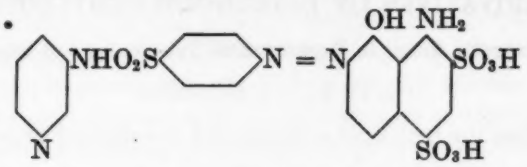


disodium formaldehyde sulfoxylate diaminodiphenylsulfone.

[1] From the Research Institute of Cutaneous Medicine, Dr. John A. Kolmer, Director, Philadelphia.

[2] Presented before the American Academy of Tuberculosis Physicians, Atlantic City, New Jersey, June 8, 1942.

The structural formula of compound No. 2816 is as follows:



4 (alpha-pyridil-N-sulfonamido) phenyl 2-azo-8-amino-1-naphthol-5,7 disulfonic acid.

Methods used: The strain of human tubercle bacilli used for all our experiments was strain A-19 of the Henry Phipps Institute in Philadelphia. Its virulence for guinea pigs was determined before beginning experimentation in order to insure the injection of a lethal dosage of bacilli. The animals were injected subcutaneously in the region of the inguinal lymph nodes with .002 g. of a fresh subculture suspended in 0.5 cc. of saline.

For our experiment, 48 guinea pigs of 300 to 400 g. were inoculated; of these, 42 were treated with the various compounds, while 6 served as controls.

Group I: 6 animals treated with sulfanilamide
Group II: 6 animals treated with sulfapyridine
Group III: 6 animals treated with sulfathiazole
Group IV: 6 animals treated with sulfathiazoline
Group V: 6 animals treated with promin
Group VI: 6 animals treated with No. 2398
Group VII: 6 animals treated with No. 2816
Group VIII: 6 untreated controls

Treatment, beginning three days after inoculation in order to give the infection a start, was continued for four weeks. The drugs were administered orally twice daily (at about 10 a.m. and 3 p.m.) in a dosage of 0.5 g. per kilogram (= 0.2 g. per animal) during the first week, and reduced by one-half, that is, 0.3 g. per kilogram (= 0.1 g. per animal) for the following three weeks. Only compound No. 2816 was employed in the smaller dosage of 0.15 g. per kilogram (= 0.05 g. per animal) throughout all our experiments. The appearance of evident toxic damage in some animals at the end of the first week of treatment accounts for the reduction in the dosage of the other 6 compounds. Promin and compound No. 2398, easily soluble in water, were administered in aqueous solution through a rubber tube, while the other compounds were given as a paste on a small spatula.

The weight of each animal was recorded twice weekly. All surviving animals were killed six weeks after infection. Autopsies were made on all animals and the degree and distribution of tuberculous lesions substantiated by direct smear examination and histological examinations.

Results: All deaths occurred from twenty-five to forty-two days after inoculation, with the exception of one animal of group I and another one of group II which died of intercurrent disease within the first week following inoculation, and one animal of group V (promin) which died on the tenth day of intoxication produced by the high oral dosage of the first week. Autopsies revealed tuberculous lesions of varying degrees but of such an extent that tuberculosis was obviously the cause of death.

At the end of the sixth week observation period, the number of survivors was as follows:

6 of the 6 treated with compound No. 2398
3 of the 6 treated with compound No. 2816
3 of the remaining 5 treated with promin
2 of each of the other 4 groups
3 of the 6 untreated controls

The distribution and degree of the tuberculous lesions, verified by examination of smears and histological sections of the tissues, demonstrated the chemotherapeutic superiority of promin and compounds No. 2398 and 2816 over the other sulfonamides used under the same conditions of experimentation. Most of the animals treated with the other sulfonamides showed wide-spread tuberculous lesions to a degree comparable to that of the untreated controls. One exceptional case was observed in the sulfapyridine group in which the surviving animal showed only the smallest degree of involvement. All controls, including those sacrificed at the end of experimentation, showed extensive lesions of tuberculosis, with the exception of one which showed only a moderate number of tubercles in the spleen, liver and lungs. Two survivors of the promin group, 2 of No. 2398 group and 1 of No. 2816 group demonstrated the inhibitory effect of these compounds by showing only a few tubercles in spleen or liver.

The graphs demonstrate the details of our histological findings, using a scale of 3 degrees according to degree of involvement: degree I indicates only a few epithelioid tubercles: degree II a moderate number of tubercles with or without central necrosis or caseation; degree III very progressed, wide-spread tuberculosis.

SECOND EXPERIMENT

In our second experiment we attempted to substantiate the results attained in the first with promin and compounds No. 2398 and No. 2816.

Methods used: The technique used in the first experiment was employed. The dosage of each of the three compounds was also the same as that used during the last three weeks of the first experiment (0.3 g. per kilo twice daily of promin and No. 2398, and 0.15 g. per kilo twice daily of No. 2816).

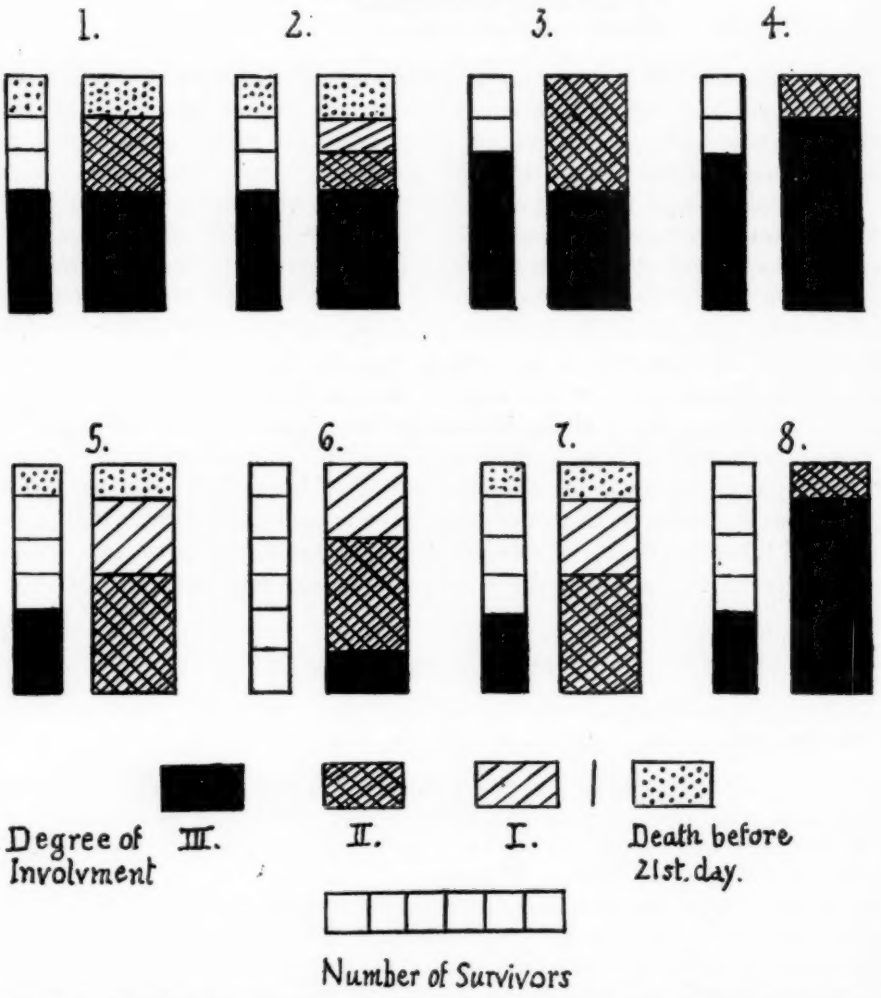
Forty-eight guinea pigs were inoculated; 9 were untreated controls, 27 were treated with compounds (9 for each of the three compounds). Administration of the latter was started three days after inoculation, according to the first experiment. The remaining 12 animals were divided into three groups of 4 animals each and were treated three days before inoculation in addition to the treatment maintained with all the other animals.

Results: At the end of the sixth week observation period, the number of survivors was as follows:

3 of the 9 untreated controls
4 of the 9 treated with promin
5 of the 9 treated with No. 2398
3 of the 9 treated with No. 2816

The parallel groups of 4 animals each which were treated beginning three days before inoculation and the following number of survivors:

1 after treatment with promin
3 after treatment with No. 2398
2 after treatment with No. 2816

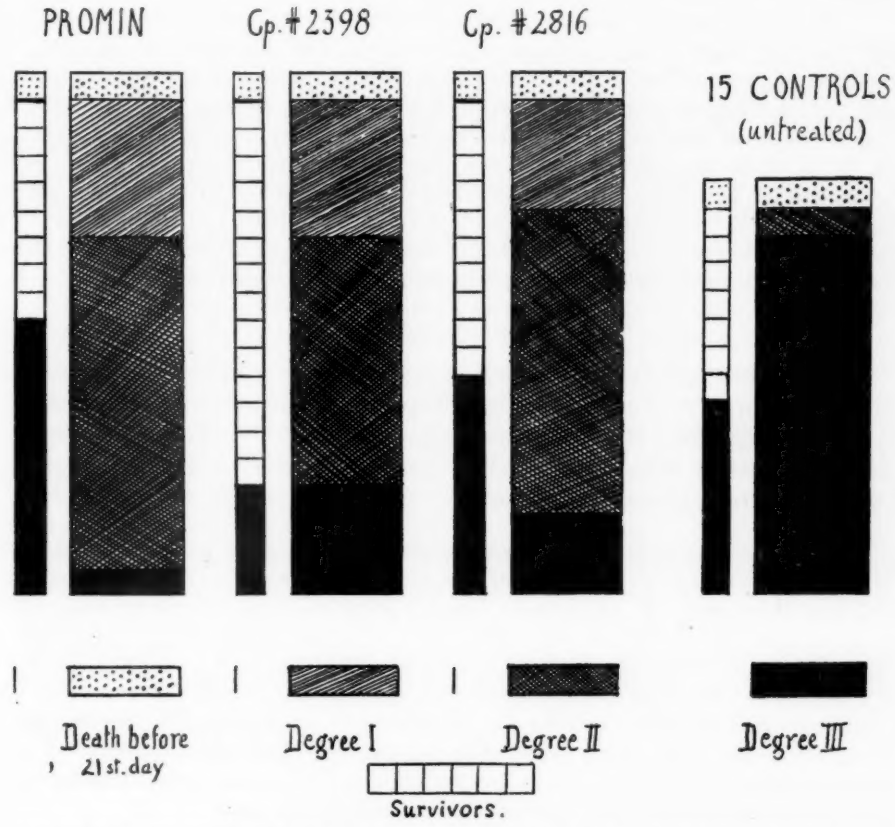


GRAPH 1. Experiment I. Mortality (small columns). Degree of Involvment (large columns). 1 = sulfanilamide, 2 = sulfapyridine, 3 = sulfathiazole, 4 = sulfathiazoline, 5 = promin, 6 = #2398, 7 = #2816, 8 = Controls.

Of the 9 untreated controls, 8 showed wide-spread tuberculosis. In comparison, only one of all the animals treated with promin (that is, 13 animals), three of all those treated with compound No. 2398 and 2 of all those treated with compound No. 2816 showed tuberculosis of a degree similar to that observed at autopsy of the control animals (degree III of the graph). The tendency toward

confluence, central necrosis and caseation seemed to be less in the treated animals, compared with the untreated controls. There was also a marked difference in the number of bacilli found in the smears and stained tissue sections of the treated compared with the untreated animals.

In all autopsies we examined the organs for evidence of toxic damage. Some animals of each group showed pathological changes, particularly of the spleen, which indicated toxic effects on the reticulo-endothelial cells. In these instances



GRAPH 2. Total mortality and degrees of involvment of the first and second experiment. (19 animals per compound.)

the size of the spleen was greatly diminished and its color was dark blue. In the first experiment we found some animals showing the same type of damage, the greatest number observed being among those treated with sulfathiazole. It is to be noted that in several of such spleens, although no tubercles were observed macroscopically, tuberculous lesions were found on microscopical examination.

Blood concentration studies: Blood concentration studies were made in all experiments. We are indebted to Mr. Herman Brown, B. S., Associate in

Biological Chemistry, of the Institute, for making these determinations. The procedure was as follows:

(*1*) To normal guinea pigs, 3 administrations of each of the various drugs of the first experiment were given within a period of twenty-four hours (at 10 a.m., 3 p.m. and 10 a.m.); 0.1 g. of the compounds promin and No. 2398 and 0.05 g. of No. 2816 were given in each dose. Blood was taken four hours after the third administration. The blood level of promin averaged between 5.6 and 5.8 mg. per 100 cc. of whole blood, of No. 2398 between 1.5 and 4.0 per 100 cc. and of No. 2816 between 1.8 and 2.6 mg. per 100 cc.

(*2*) To normal guinea pigs, two administrations daily of promin, No. 2398 and No. 2816 were given for five days; 0.1 g. of promin and No. 2398, and 0.05 g. of No. 2816 were given in each dose. The blood was taken twice: in the afternoon of the fifth day immediately before the last administration, and in the morning of the sixth day just before the time of the usual administration. The blood concentration of promin was 6.7 mg. per 100 cc. of whole blood in the afternoon of the fifth day and 2.4 mg. per 100 cc. in the morning of the sixth day. No. 2398 produced a concentration of 4.9 and 1.7 mg. per 100 cc., and No. 2816 a concentration of 3.0 and 1.2 mg. per 100 cc. of whole blood. The second set of determinations indicated that there was no appreciable difference between the results of a twenty-four-hour administration and a five-day treatment.

THIRD EXPERIMENT

In our final experiment we administered the three compounds promin, No. 2398 and No. 2816 parenterally by intramuscular injection of oil suspensions prepared by grinding the respective drugs in peanut oil. We intended to produce a deposit of drug from which a slower absorption and a more constant blood concentration could be expected.

Methods used: For this purpose it was necessary first to grind each compound as fine as possible (200 mesh). The amount of oil necessary for preparing the suspensions varied with each compound. To administer a five-day dosage corresponding to the dosage given orally we added: 0.7 cc. peanut oil to 1.0 g. promin (= 5 daily doses of 0.2 g. given orally), 1.2 cc. peanut oil to the same amount of compound No. 2398, and 1 cc. peanut oil to 0.5 g. of compound No. 2816 (= 5 daily doses of 0.1 g.). These suspensions were of such consistency that we could inject them through a needle of 20 gauge. We injected deeply into the muscles of the thighs, alternating between the right and left, every five days. Only the fifth injection had to be administered to a few animals in the muscles of the forelegs in order to prevent too extensive damage of the muscles.

Twenty-four guinea pigs of 400 to 500 g. were inoculated with 2 mg. of bacilli. Six animals served as untreated controls and 18 were treated as follows: 6 with injections of promin, 6 with compound No. 2398, and 6 with compound No. 2816. The first injection was given three days after inoculation, the second five days after the first. After having found obvious toxic changes of the spleen in autopsies of three guinea pigs which died after treatment with two injections of promin and No. 2398, we postponed the next injection until ten days after the second, continuing the treatment by half the dosage every five days. Five injections were given within the treatment period of four weeks. The survivors were sacrificed six weeks after infection.

Results: Several deaths due to toxic effects apparently produced by the dosage of the first and second injections, restrict the results attained. At autopsy,

2 animals of each group showed the significant diminuation in the size and the dark blue hue of the spleen. This damage was verified microscopically by changes observed in the reticulo-endothelial cells of the organ. Disregarding these cases, we considered only 4 animals of each compound. The number of survivors was as follows:

2 of 6 untreated controls
2 of 4 treated with promin
2 or 4 treated with No. 2398
1 of 4 treated with No. 2816

All untreated controls showed advanced, wide-spread tuberculosis verified by microscopical examination. In comparison, one of the survivors of the promin-treated animals, and one of the No. 2398 group showed only a few tubercles in spleen or liver.

Most of the treated animals showed no considerable disturbance of activity and, if so, only a transitory disturbance of a few hours, or at most of one or two days. Promin injections were tolerated without remarkable inflammatory tissue reaction; injections of No. 2398 produced inflammatory induration around the deposit which persisted for ten to fourteen days; injections of No. 2916 were tolerated the least because of the production of abscesses. In 3 guinea pigs treated with No. 2816 necrosis of the muscle walls of the cavities occurred.

At autopsy we could study both the degree of absorption and the local effect of these compounds on the tissues. After seventy-two hours, the incised intramuscular cavities were nearly empty of promin, but half filled with the residue of the thicker suspension of compound No. 2398 which was absorbed after ten to fourteen days.

In spite of this evident absorption, blood concentration determinations made on both free or acetylated sulfonamides failed to show the course of absorption of promin and compound No. 2398. The results were negative with the methods used. We have no explanation for this observation. Only compound No. 2816 gave positive results, with a blood concentration after twenty-four hours of 1.2 to 1.4 mg. per 100 cc. of whole blood; after seventy-two hours the results were negative. Investigation is to be continued.

COMMENT

In evaluating the results obtained in our experiments we must take into consideration: (*1*) the number of deaths within the six-week period of observation, and (*2*) the extent of the disease as determined by autopsies and histological examination.

We do not wish to evaluate the results attained in animals dying before the twenty-first day after infection, since we feel that this period of time is too short for evaluation of the degree of involvement; therefore, we must disregard one animal from each of the groups treated with sulfanilamide, sulfapyridine, promin, No. 2398 and No. 2816.

We have interpreted the results attained under the conditions of our experiments as indicating a chemotherapeutic superiority of promin and compounds

No. 2398 and No. 2816 over sulfanilamide, sulfapyridine, sulfathiazole and sulfathiazoline. These three compounds, in varying degree, appeared to be capable of inhibiting the involvement and of preventing the spread of experimental tuberculosis. The other compounds did not show such beneficial effects under the same conditions of experimentation.

In untreated controls of the first and second experiments, 13 of 15 animals showed wide-spread tuberculosis of degree III; in comparison, most of the treated animals showed degree I or degree II. Only 1 of the 18 promin-treated animals showed degree III in autopsy, 4 of 18 treated with compound No. 2398, and 2 of 18 treated with compound No. 2816. Within the observation period of six weeks, which we chose according to Rich and Follis (15, 16), we found significant differences between the histology of the treated and untreated animals. Our findings were comparable with those of Feldman and Hinshaw (8) who followed the development of these changes through several months in promin-treated animals.

The mortality observed after the twenty-first day following inoculation is as follows:

10 of 18 animals treated with promin
4 of 18 animals treated with No. 2398
8 of 18 animals treated with No. 2816
8 of 15 untreated controls

Compound No. 2398, therefore, was responsible for the smallest percentage of deaths, although given in the same dosage as promin. Concerning the high mortality observed with promin, we feel that some deaths were obviously due to the toxic effect of the dosage used during the first period of experimentation. (One guinea pig, promin-treated, which died on the tenth day, showed rapid loss of weight, weakness and paralysis of the hind legs, observed two to three days before death. Autopsy showed the spleen to be very small and of dark blue color. Histological examination of the lumbar region of the spinal cord showed alteration of the ganglion cells, vacuolization of cytoplasm, loss of stainability and loss of contrast between nucleus and cytoplasm. These symptoms and signs seemed to indicate chemical intoxication, comparable with changes described by Friedman and Shienfeld (9) in human sulfarsphenamine encephalitis.) We attempted to administer promin orally in a dosage corresponding to the reports in the literature; however, there was soon an obvious difference between the tolerance of the dosage given in the food by Feldman and Hinshaw and the tolerance of the same dosage administered in two parts daily, orally.

As to our experiment, based on parenteral administration by intramuscular injection of oil suspensions, we do not include it in our results, except with reservation, because the number of deaths was too great. The histological examination of the small number of sacrificed survivors, however, gave results similar to those of our other experiments and definitely contrasted with the wide-spread tuberculosis of the untreated controls. This route of administration had not yet been tried by American investigators in sulfonamide treatment of experimental tuberculosis of guinea pigs. Rist, Bloch and Hamon (17), of the

Pasteur Institute in Paris, injected oil suspensions subcutaneously in rabbits infected with an avian strain of tubercle bacilli, showing the effectiveness of the parent diaminodiphenylsulfone. This route of administration may be of interest in further experimentation.

SUMMARY

1. Under the conditions of our experiments, the derivatives of diaminodiphenylsulfone-promin, compound No. 2398 and No. 2816—produced evident inhibition of the development of experimental tuberculosis in guinea pigs.

2. Sulfanilamide, sulfapyridine, sulfathiazole and sulfathiazoline showed no appreciable effect under the same conditions of experimentation.

3. When histological changes alone are considered, promin produced the most favorable results. The highest mortality, however, was observed with promin treatment with the dosage employed.

4. Compound No. 2398 produced almost as favorable results, histologically, with the lowest mortality of the three compounds.

5. Compound No. 2816 produced results similar to those of No. 2398, but with mortality almost as great as that of promin, even though given in a smaller dosage.

6. The preventive administration of the three compounds did not enhance their effectiveness.

7. When both mortality and histological change are considered, compound No. 2398 produced the most beneficial results in our experiments.

We feel that our investigation provides encouraging data for further study on the comparative effectiveness of promin and compound No. 2398.

SUMARIO

1. En las condiciones de estos experimentos, los derivados de la diaminodifenilsulfón-promina y compuestos No. 2398 y No. 2816—produjeron manifiesta inhibición de la tuberculosis experimental en el cobayo.

2. La sulfanilamida, la sulfapiridina, el sulfatiazol y la sulfatiazolina no mostraron efecto apreciable en las mismas condiciones de experimentación.

3. Considerando únicamente las alteraciones histológicas, la promina fué la que produjo resultado más favorable, pero a la dosis empleada también le correspondió la mortalidad máxima.

4. De los tres compuestos el No. 2398 fué el que produjo resultados casi tan favorables histológicamente, con la mortalidad mínima.

5. El compuesto No. 2816 produjo resultados semejantes a los del No. 2398, pero con una mortalidad casi igual a la promina, aunque administrado a dosis más pequeñas.

6. La administración profiláctica de los tres compuestos no acrecentó su eficacia.

7. Considerando tanto la mortalidad como las alteraciones histológicas, el compuesto No. 2398 fué el que produjo más beneficio en estos experimentos.

Esta investigación parece aportar datos que alientan el estudio ulterior de la eficacia comparada de la promina y del compuesto No. 2398.

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Cases presented at the Diagnostic and Therapeutic Clinical Conference arranged by the American Trudeau Society, under the Chairmanship of Dr. Henry C. Sweany

PRIMARY ASPERGILLOSIS OF THE LUNGS[1]

LEON H. HETHERINGTON[2]

A thirty-three year old male, employed as a manager of a luggage business, was first seen on April 20, 1938. His symptoms had started two years before with cough, unexplained loss in weight and mild dyspnoea. One year after the onset of his symptoms, he had an attack of pleurisy which lasted a week. The cough at first was nonproductive but later became severe and he began to raise a black, mucoid sputum. There was a loss of thirty pounds in weight. The dyspnoea became progressively worse.

He had two attacks of renal colic, one in 1935 and one in 1938. On both occasions calculi were expelled spontaneously. He had had measles and diphtheria in childhood and had been quite ill with influenza at the age of fourteen. His habits were good. His entire life had been spent in Pittsburgh with the exception of two years when he attended college at Ann Arbor, Michigan. He gave no history of exposure to pigeons and had had no unusual contact with grain. His family history was irrelevant.

On physical examination, the patient's temperature was 98.6°F.; his pulse, 84 and he weighed 150 pounds. Examination was essentially negative except for a few, moderately coarse râles in the interscapular regions on both sides. His blood pressure was 100/70. Tuberculin tests, using both strengths of PPD, were negative. He was also negative to a full milligram of OT. Approximately twenty sputum examinations were negative for tubercle bacilli. An occasional specimen showed some mycelial threads. The blood studies were within normal limits.

Stereoscopic X-ray films revealed a bilateral pulmonary lesion, first interpreted as an extensive, bilateral tuberculosis with marked diaphragmatic adhesions. The distribution of the lesions suggested the possibility of an underlying silicosis.

In cultures of the sputum on Sabourauds media, a mold grew which was reported as *Penicillium glaucum*. However, subsequent cultures were reported as *Aspergillus niger*. The patient was given iodids but was unable to tolerate them because of severe gastric disturbances. His cough became very troublesome and he continued to get worse. A diagnosis of primary aspergillosis of the lungs was made. Consultation opinions were requested which resulted in one diagnosis of pneumonoconiosis and one of secondary sarcomatosis with questionable

[1] Presented before the Medical Section at the 38th annual meeting of the National Tuberculosis Association, Philadelphia, Pennsylvania, May 8, 1942.

[2] Tuberculosis League Hospital, Pittsburgh, Pennsylvania.

primary growth in the left upper quadrant of the abdomen. X-ray therapy was recommended and was carried out for six months without benefit. An autogenous vaccine was prepared and given the patient at weekly intervals during the time he was treated with X-ray. He continued to get worse. He was then placed on thymol-iodid, following which he began to expectorate large quantities of thick, green, purulent material without odor. His temperature, which had had remained normal until then, ranged from 100° to 101°F. Physical signs now showed evidence of extensive pulmonary infection with cavitation. He died in November, 1939.

Permission was granted for postmortem examination of the lungs only.

The lungs were greatly increased in size and weight. The pleura was considerably thickened in the upper half. Externally, the lungs were mottled gray bluish with small, minute areas of dark haemorrhage.

Cut-section showed bronchial thickening. There was increased pearly-gray to black interstitial connective tissue in the upper half of the lung, especially about the bronchi, cavities and beneath the pleura. The cavities were about two inches in diameter. They occurred in the upper half of the lung and preferred the subpleural zone. These cavities had ragged grayish-black walls that measured 3 mm. in thickness. Nodular grayish-black areas were present near the cavities. These were about 2 cm. in diameter and contained caseous contents which could be expressed. In the lower half of the lungs there were many small, dilated spaces, about 1 mm. in diameter, which gave the lung a sponge-like appearance. Some of these spaces were filled with a clear gelatinous substance while others were dark red in color. The hilar lymph nodes were enlarged, grayish-black and putty-like in consistency.

Microscopical sections showed an interstitial increase of connective tissue with local infiltration of lymphocytes, calcium deposits and anthracotic deposits. The contents of the alveolar spaces varied from serous fluid to collections of polymorphonuclears, lymphocytes, monocytes and red blood corpuscles to formation of connective tissue. Scattered areas of caseation were seen with central karyolysis and karyorrhexis and peripheral collections of polymorphonuclears, lymphocytes and monocytes.

In some of the sections, dense mats of mycelial threads were to be seen. These had a scattering of fruiting bodies. From the central knob-like projection, rows of phialiades radiated. Chains of spores extended peripherally. These were characteristic of aspergillosis.

Anatomical diagnosis: aspergillosis.

In view of the clinical, anatomical and bacteriological findings, a diagnosis of primary *Aspergillus niger* infection of the lungs seemed justified.

PRIMARY CARCINOMA OF THE BRONCHUS ASSOCIATED WITH FOREIGN BODY[1]

J. M. BLAKE[2]

The relationship of carcinoma to chronic irritation has always been of interest. The case presented here is interesting in view of the fact that a chronic irritating factor was present for a number of years with subsequent development of primary bronchogenic carcinoma at the sight of the irritant.

This patient, a fifty-six year old white Lithuanian male, a machinist, was referred for examination on July 3, 1941 because of a mild cough and wheezing in his chest. His family history is irrevalent.

The past history is interesting in regard to a slight cough which had been present for several years, but which did not cause him any great discomfort and was considered to be insignificant.

His present history dates to November, 1940 at which time he received a rather severe blow to the left side of his chest. This did not cause incapacitation and was considered of no significance. Shortly following this, however, he developed an acute respiratory infection which similated an ordinary bronchitis. His symptoms, however, persisted and he consulted his family physician. At that time he had a moderately severe cough, expectoration and elevation of temperature to 103°F. There was also some blood-streaked sputum during this period and he was moderately ill with malaise and lassitude. Hospitalization was advised by his physician who suspected a possible pneumonia.

X-ray examination after hospitalization was reported to the physician as negative (subsequent review of this X-ray film showed a rounded density in the lower portion of the right lung 3 x 3 cm. in diameter (figure 1).

He seemed to recover from his acute illness, his temperature became normal and he returned to his home. The cough persisted however and he did not feel as well as usual. Gradual loss of weight was noted to a total of 15 pounds. These symptoms of fatigue, cough and expectoration seemed to increase gradually to the time he was referred here.

Physical examination in July, 1941 showed impaired resonance and diminished breath sounds from the third rib to the diaphragm and in the axilla on the right side. A few coarse râles and wheezes were also heard in the area of the middle lobe.

Fluoroscopic and X-ray examination at this time showed a dense, hazy area involving the lower portion of the right lung in the region of the middle lobe. The findings suggested bronchial obstruction, partial atelectasis and possibly some suppuration.

[1] Presented before the Medical Section at the 38th annual meeting of the National Tuberculosis Association, Philadelphia, Pennsylvania, May 8, 1942.

[2] Schenectady County Tuberculosis Hospital, Schenectady, New York.

Urinalysis, Wassermann and Kline tests were negative. Blood count: red cells, 5,400,000; haemoglobin, 92 per cent; while cells, 15,200; neutrophils 68 per cent, lymphocytes 22 per cent, monocytes 7 per cent, eosinophils 2 per cent, basophils 1 per cent. Sedimentation time: 39 minutes (Linzenmeier).

Bronchoscopic examination revealed thickening and widening of the carina with limitation of motion. The right middle-lobe bronchus was almost completely occluded by a granular mass 1 cm. from the orifice; a preliminary diagnosis of bronchogenic carcinoma of the right middle-lobe bronchus was made.

A biopsy was taken and the tissue removed was considerably larger than anticipated. Pathological examination of the biopsy material revealed a small metal

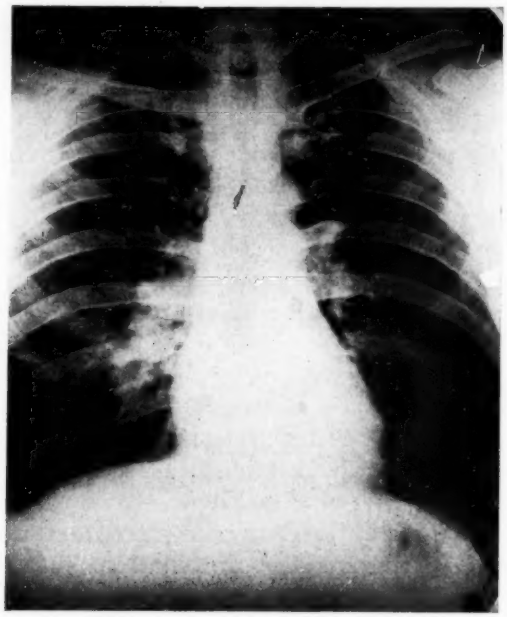

FIG. 1

crucifix, measuring 4 x 7 mm., imbedded in the tissue. A diagnosis of carcinoma was made from the tissue.

Exploratory thoracotomy was done which revealed an inoperable anaplastic carcinoma of the right middle lobe. The carcinomatous tissue was found to involve the pericardium, the great vessels and mediastinal lymph nodes.

Postoperative convalescence was uneventful.

The patient did not give any preliminary history of a foreign body, but, following the discovery in the biopsy material, further questioning revealed that about six years previously he had lost a small metal crucifix which he thought he had swallowed.

The crucifix could not be seen on the X-ray films before and after its presence was known by the various physicians who reviewed the X-ray films.

Since the carcinoma was inoperable, deep X-ray therapy was given in the usual

dosage and manner, but no benefit was derived from this. The lobe became completely obstructed and gradual decline in the patient's condition was noted. He subsequently developed clinical symptoms of metastases to the left temporal lobe of the brain and expired approximately nine months after the diagnosis had been made. Unfortunately an autopsy could not be obtained, but the clinical symptoms of metastases were quite definite.

SUMMARY

This patient presents two interesting features, the first being the probability of the relationship of the foreign body in the bronchus and associated chronic irritation to the subsequent development of carcinoma at the site. The second feature is that the metal crucifix did not cast a demonstrable shadow in the X-ray films.

ARMY X-RAY EXAMINATION FOR TUBERCULOSIS[1, 2, 3]

Army Physical Examination Teams in Southern New York District, Second Corps Area

DAVID E. EHRLICH,[4] ISRAEL A. SCHILLER[5] AND HERBERT R. EDWARDS[6]

A review of routine X-ray examination of National Guardsmen and Selective Service Registrants in the Southern New York District of the Second Corps Area from November 25, 1940 to April 1, 1941 was reported by Edwards and Ehrlich (1).

The purpose of this presentation is threefold. First, to report the findings with the 14″ x 17″ paper chest film between April 1 and June 1, 1941. Second, the results of X-ray examination with the 4″ x 5″ photo-roentgenogram between June 1 and October 31, 1941. Third, to indicate the contribution made by the Bureau of Tuberculosis of the New York City Department of Health in the evaluation of cases rejected by the Army Physical Examination Teams on the basis of pulmonary lesions revealed by X-ray examination. A brief review of the procedures used in this work will assist in the evaluation of the results obtained.

After registration and preparation for physical examination, the registrant is routed to the X-ray unit so that his chest X-ray film is taken and interpreted by the time the rest of the examination is complete. The method employed with the paper film has been described in detail by Edwards and Ehrlich (1). The method employed with the 4″ x 5″ photo-roentgenogram is essentially the following: At the beginning of the examination an X-ray tag containing the registrant's name, address, film and identification numbers are typewritten on a bulletin-type machine for purposes of X-ray identification. This tag is inserted by the X-ray technician into a holder which fits into a slot at the upper corner of the chest piece, so that it is photographed on the film in reduced size by the rays from the fluorescent screen. The registrant is then x-rayed and continues with the rest of the examination.

The photo-roentgen unit (2) is a light-proof box, the front end of which is concave to fit the chest and contains the fluoroscopic screen, while the rear end is essentially a camera with a reducing lens between the screen in front and the film behind. The film is of the high-speed X-ray type and is loaded in a two-film holder which fits into a slot at the back of the camera. A flexible slide cover fits over the face of the film and is easily removed or replaced before and after exposure. The tube-screen distance is constant at 40 inches and the necessity of adjusting for the height of the subject has been eliminated by using a step arrangement on which the registrant may stand while being X-rayed. The apparatus is powered by a 200 M.A. unit, with an oil-immersed tube, using a focal spot of 5.2

[1] Read by Major D. E. Ehrlich at the 32nd Annual Midwinter Eastern Conference of Radiologists, at the Hotel Biltmore, New York, New York, January 23, 1942.

[2] Read by Major I. A. Schiller before the Long Island Radiological Society, at the Kings County Medical Society Building, Brooklyn, New York, January 22, 1942.

[3] The views expressed in this article represent the personal opinions of the authors, and are not to be regarded as a statement of War Department policy.

[4] Major, Medical Corps.

[5] Major, Medical Corps.

[6] Director, Bureau of Tuberculosis, New York City Department of Health.

mm. For a chest of average thickness, our technique consists of $\frac{3}{10}$ of a second at 200 M.A. and 70 K.V.

After exposure, the films are loaded into grooved and hinged film hangers, each accommodating six films. When developed, they are passed from the dark room into a two-door hot air drying cabinet whence they are removed into the X-ray reading room and read while still wet. If the 4″ x 5″ film reveals a lesion or a suspicion of an abnormal shadow, a 14″ x 17″ acetate film can be made at once and also read in the wet state.

In all this work, the Southern New York Army Physical Examination Team has had the close and valuable coöperation of the Bureau of Tuberculosis of the New York City Department of Health in studying and following up registrants rejected for pulmonary disease. Because of this collaboration, it has been possible subsequently to reclaim a small but definite percentage of men who were rejected initially because of suspicious shadows, or who had conditions such as bronchopneumonia which were only temporarily disqualifying. In addition, it has been possible to compare the results obtained by various X-ray methods. Appreciating the great public health value of the X-ray program as carried out at Army Examining Stations, the military medical personnel have endeavored to collaborate with other public health agencies by reporting cases of tuberculosis.

A rejected registrant who resides in New York City is given a referral slip to the Central Chest Clinic of the New York City Health Department on which the date, time and place of the appointment are clearly stated. When the registrant reports to the Chest Clinic, he is studied completely; a history is taken, physical examination and fluoroscopy are performed, further X-ray films made and, where indicated, bronchography by instillation of iodized oil is carried out. Sputum examination and other indicated laboratory procedures are also done. Upon completion of the work-up of the case, the Central Chest Clinic informs the local board of its conclusions and its recommendations. In the event that the registrant is found to be in need of medical care or hospitalization the coöperation of the local board is solicited by the Department of Health.

Should the registrant reside outside of New York City, the X-ray film is forwarded to his local draft board with a letter requesting that the film be made available to his private physician and his name is reported to the State Department of Health.

The criteria for rejection on the basis of the chest X-ray are as stated in MR 1–9, with the exception that registrants who show evidence of reinfection or adult type of tuberculosis are not accepted for induction regardless of the extent of the lesion. These criteria have been modified recently (2). In addition to tuberculosis, such conditions as bronchiectasis and extensive adhesive pleurisy or pulmonary fibrosis constitute cause for rejection, while acute conditions, such as pneumonia, pleural effusion and spontaneous pneumothorax, will also bar a man from acceptance for Army service. More rarely encountered conditions such as hilar or mediastinal adenopathy, neoplasms of whatever origin, diaphragmatic abnormalities or bizarre cardiac contours will also exclude the registrant. Well calcified childhood tuberculosis, if not extensive, is acceptable, while cases with disseminated discrete calcific nodules are excluded as cases of healed haematogenous tuberculosis.

Up to October 31, 1941, the Health Department and the Army Examining Teams in New York City and Governors Island X-rayed the chests of 114,130 men, of which 9,541 were National Guardsmen who were to be inducted into

Federal Service, and 104,589 were Selective Service Registrants. Of this total, 1,304 men, or 1.14 per cent, were rejected as unsuitable for army service because of pulmonary lesions. Of this total, 1,156 were diagnosed pulmonary tuberculosis, the remainder, 148, being nontuberculous in aetiology (table 1). Four hundred and thirty-five, or 37 per cent of the tuberculosis cases, were considered at the time to be clinically significant and in need of further study and care. Seven hundred and twenty-one, or 63 per cent, were found after study to be arrested. In terms of percentage of the entire number of men examined, the incidence of chronic pulmonary tuberculosis was 1.01 per cent, of which 0.38 per cent were on subsequent analysis considered to be active and 0.63 per cent arrested. In comparison, the nontuberculous cases constituted only a very small part of the group, 0.13 per cent. Of the active cases of tuberculosis, 50

TABLE 1

Results of X-ray examinations of Selective Service Registrants and National Guardsmen Southern New York District

UNIT	NUMBER						PERCENTAGES				
	Number X-rayed	Rejected for pulmonary conditions	Pulmonary tuberculosis			Other pulmonary	Rejected for pulmonary conditions	Pulmonary tuberculosis			Other pulmonary
			Active	Arrested	Total			Active	Arrested	Total	
National Guard.....	9,541	115	41	56	97	18	1.21	0.43	0.59	1.02	0.19
Selectees to January 16, 1941.....	6,609	90	29	46	75	15	1.36	0.44	0.70	1.13	0.23
Selectees January 16 to October 31, 1941.....	97,980	1,099	365	619	984	115	1.12	.37	.63	1.01	0.12
Totals.....	114,130	1,304	435	721	1,156	148	1.14	0.38	0.63	1.01	0.13

per cent proved to be minimal, 43 per cent moderately advanced and 7 per cent far advanced.

An examination of the figures by periods (table 2) shows that up to June, 1941, the rate of rejections for pulmonary disease varied between 1.2 per cent and 1.36 per cent, but that subsequent to June 1 the rejection rate fell to 0.88 per cent and that this change occurred chiefly as a result of a decline in the prevalence of arrested tuberculosis, the prevalence of active or clinically significant tuberculosis and nontuberculous disease remaining essentially the same as in previous months. About June 1, 1941 the number of men over twenty-eight years of age sent for examination began to decline rapidly in anticipation of the passage by Congress of the amendment to the Selective Service Law exempting men over twenty-eight from Army service. In fact, after July 1, all selectees examined were under twenty-eight years of age.

Selective Service authorities estimate that prior to July 1, 1941, men over twenty-eight constituted about 28 per cent of all registrants sent for pre-induction examination. We see, therefore, that this fall in the rejection rate may be related to the elimination from our material of the men between the ages of twenty-eight and thirty-five, a group which formerly constituted over a quarter of the registrants examined. The increase in the prevalence of tuberculosis with increasing age has been repeatedly demonstrated and is borne out in the study of 9,541 National Guardsmen and 6,609 selectees by Edwards and Ehrlich (1), in which the incidence of tuberculosis was found considerably higher in men over twenty-eight, especially as regards the proportion of arrested cases.

TABLE 2

Result of X-ray examinations of Selective Service Registrants and National Guardsmen by periods

Southern New York District

UNIT	NUMBER						PER CENT				
	Number X-rayed	Rejected for pulmonary conditions	Pulmonary Tuberculosis			Other pulmonary	Rejected for pulmonary conditions	Pulmonary tuberculosis			Other pulmonary
			Active	Arrested	Total			Active	Arrested	Total	
National Guard.....	9,541	115	41	56	97	18	1.21	0.43	0.59	1.02	0.19
Selective Service to 1/16/41.....	6,609	90	29	46	75	15	1.36	0.44	0.70	1.13	0.23
January 16 to March 31, 1941.....	35,210	424	143	252	395	29	1.20	0.41	0.72	1.12	0.08
April 1 to May 30, 1941.....	28,235	371	110	226	336	35	1.31	0.39	0.80	1.19	0.12
June 1 to October 31, 1941..	34,535	304	112	141	253	51	0.88	0.32	0.41	0.73	0.15
Totals	114,130	1,304	435	721	1,156	148	1.14	0.38	0.63	1.01	0.13

In an attempt to determine whether the change in the age distribution of men examined after June 1 could explain the fall in the rejection rate noted at this time, we have compared the men X-rayed after July 1, 1941 on 4″ x 5″ film with a group of men X-rayed in April, May and June on 14″ x 17″ paper X-ray films. In the 4″ x 5″ film method, no men over twenty-eight were included, as they were no longer being sent for examination. In the paper film method, suitable deductions were made to exclude the cases of tuberculosis in men over twenty-eight, using the experience of Edwards and Ehrlich (1) to calculate the incidence of tuberculosis in this older age group. The incidence of tuberculosis in men under twenty-eight was thus estimated for the group examined by the 14″ x 17″ paper method. The results of this comparison are shown in table 3. We have

for the paper method a group of 20,329 men and for the celluloid 4″ x 5″ method a comparable group of 25,506. The rejection rate for tuberculosis was 0.70 per cent in the 4″ x 5″ group, and 0.88 per cent in the paper group. Statistical analysis of these figures shows that the difference between them is not significant. This comparison would thus tend to support the hypothesis that the fall in the rejection rate noted with the 4″ x 5″ method could be explained by the elimination from consideration of men over twenty-eight after July 1, 1941.

TABLE 3

Comparative findings among Selective Service Registrants using 4″ x 5″ fluorography and 14″ x 17″ paper—21–28 year age group
Southern New York District

MEDIUM	NUMBER				PER CENT		
	Number X-rayed	Pulmonary tuberculosis			Pulmonary tuberculosis		
		Active	Arrested	Total	Active	Arrested	Total
4″ x 5″	25,506	85	94	179	0.33	0.37	0.70
Paper	20,329	74	99	173	0.36	0.49	0.88

TABLE 4

Rejections for pulmonary conditions other than tuberculosis

Bronchiectasis	57
Pleural lesions	21
Spontaneous pneumothorax	13
Mediastinal lymphadenopathy	12
Cysts and tumors	12
Pneumonias	11
Fibrosis	8
Pneumonoconiosis	4
Undetermined lesions	4
Bronchial stenosis	2
Diaphragmatic hernia	2
Congenital heart abnormalities	2
Total	148

A brief glance at our nontuberculous group should be interesting (table 4). Of these 148 cases, bronchiectasis contributes 57 cases of which 54 were proved by bronchography. Disease of the pleura is the next largest group, with 21 cases. Spontaneous pneumothorax and mediastinal lymphadenopathy constituted 13 and 12 cases, respectively. It might be noted in this connection that there were 4 cases of Boeck's sarcoidosis in the latter group. Cysts and tumors each accounted for 12 cases and the pneumonia group for another 11. The incidence of pneumonia should be somewhat higher, as the pneumonias that cleared up under observation and were recertified are not included among the rejected cases. It might be more accurate to speak of these 11 cases as atypical

pneumonia or pneumonitis. Eight cases of pulmonary fibrosis and 4 of pneumonoconiosis are next noted. In 4 cases the cause of the lesion was not determined. Bronchial stenosis, diaphragmatic hernia and congenital heart disease each occurred twice.

An interesting comparison of the two methods of X-ray survey is offered by the percentage of rejected men who later were found acceptable for military service on more complete study after preliminary rejection by the Army Examining Team. It has always been the aim of the examining teams to be extremely conservative in accepting men who showed suspicious shadows on their chest X-ray films. In this regard it has been deemed advisable to reject temporarily registrants who show suspicious lesions and to have the Health Department study such cases more completely before deciding their acceptability for military service.

This attitude of conservatism in border-line cases was intensified with the advent of the 4″ x 5″ photo-roentgenogram, since this was a new method of screening to all the roentgenologists engaged in this work. The 14″ x 17″ method, on the other hand, was one with which the examing team personnel were thoroughly familiar because of long previous experience.

TABLE 5

Comparison of recertification rate of 14″ x 17″ paper film and 4″ x 5″ photo-roentgenogram

MEDIUM	NUMBER X-RAYED	NUMBER REJECTED	NUMBER RECERTIFIED	PER CENT RECERTIFIED
Paper	28,235	409	38	9.3
4″ x 5″	32,372	346	61	17.6

It was therefore to be expected that the percentage of men found acceptable after complete study was greater with the 4″ x 5″ photo-roentgenogram than it was with the more familiar 14″ x 17″ paper film (table 5). With the latter method, 9.3 per cent of men rejected subsequently were certified as fit for Army service after study by the Central Chest Clinic, while with the newer 4″ x 5″ method, 17.6 per cent of men rejected later proved to be acceptable after complete work-up. It should be borne in mind that many cases subsequently found fit for Army service had temporary disabilities such as bronchopneumonia, or histories suggestive of other pulmonary disease which required observation and further study at the time of their original examination by the Army Examining Team. These cases, therefore, do not represent diagnostic errors. They should be regarded rather as the inevitable result of a conservative attitude on the part of the X-ray readers, especially with the more recent method of screening, in dealing with a mass of material containing numerous border-line cases as well as temporarily disqualifying conditions. Recognizing the problem offered by border-line cases which require further observation before a decision as to acceptability can be rendered, the War Department has recently designated a classification "1A (suspended)" to include men in this category.

A few words are in order as to the public health and financial aspects of this work. It should be pointed out that the vast majority of cases that are found in the course of Army physical examinations are new and previously unregistered. The advantage to the Army and the community of the early segregation of tuberculous individuals and of prompt treatment to the patient cannot be estimated in terms of dollars. In terms of economic and human values this part of the Army X-ray program is of inestimable value to the nation and the individual. While it tells only part of the story, the dollars and cents aspect of this work may be appraised by taking Spillman's (3) estimated cost to the government of $10,000 for every man with tuberculosis inducted into the armed forces. On this basis, the estimated saving to the government by reason of the exclusion of these 1,300 cases out of the total of 114,130 examined would be $13,000,000. The future will, undoubtedly, amply justify the foresight and wisdom of the War Department in requiring a chest X-ray film for every individual entering active military service.

CONCLUSIONS

1. Since the beginning of Selective Service examinations to October 31, 1941, 114,130 Selective Service registrants and National Guardsmen have had chest X-ray films by the Army Physical Examination Teams of the Southern New York District.

2. Of this total, 1,304, or 1.14 per cent, were rejected under MR 1–9.

3. One thousand one hundred and fifty-six, or 1.01 per cent, were classified as chronic pulmonary tuberculosis. Of these, 435, or 0.38 per cent, were classified as clinically significant and 721, or 0.63 per cent, as arrested.

4. Following a complete study of rejected cases by the New York City Health Department it was found that the percentage reclassified as acceptable for Army service after previous rejection on the basis of the paper film was half that of those disqualified on the basis of the 4″ x 5″ film. This evidence would suggest that the screening by the 4″ x 5″ photo-roentgenogram required greater conservatism in interpretation than the 14″ x 17″ paper X-ray.

5. The active part taken by the Bureau of Tuberculosis of the Department of Health with the Army authorities in the follow-up of these cases offers what may be considered an ideal program in the control of tuberculosis in men to be inducted into the armed forces.

6. The financial saving to the Federal Government in the elimination from service of those with known tuberculous lesions may be estimated at $13,000,000.

CONCLUSIONES

1. Desde que se iniciaron los exámenes del Servicio Selectivo, hasta el 31 de octubre de 1941, las Juntas de Exámenes Físicos del Ejército, del distrito meridional de Nueva York, han obtenido 114,130 películas torácicas de candidatos al Servicio Selectivo y de miembros de la Guardia Nacional.

2. Del total, 1,304, o sea 1.14 por ciento, fueron rechazados de conformidad con la orden MR 1–9.

3. Mil ciento cincuenta y seis (1.01 por ciento) fueron clasificados como tuberculosos pulmonares crónicos, y de éstos, 435 (0.38 por ciento), fueron clasificados como de importancia clínica y 721 (0.63 por ciento), como estacionados.

4. Tras un estudio detenido de los casos rechazados por el Departamento Municipal de Sanidad de Nueva York, descubrióse que el porcentaje reclasificado como aceptable para el servicio militar, después de haber sido rechazado basándose en la película de papel, ascendía a la mitad de los rechazados tomando por base películas de 4 x 5. Estos datos indican que hay que mostrarse más conservador al interpretar el fotorroentgenograma de 4 x 5 que el papel de 14 x 17.

5. La participación activa de la Oficina de Tuberculosis del Departamento de Sanidad con las autoridades militares en la investigación subsecuente de estos casos, ofrece lo que puede considerarse como un programa ideal para el control de la tuberculosis en los individuos que van a ingresar en las fuerzas armadas.

6. Calcúlase en 13,000,000 de dólares el ahorro que representa para el Gobierno Federal el rechazo del servicio de individuos con lesiones tuberculosas conocidas.

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COMBATING TUBERCULOSIS IN UNION OF SOCIALIST SOVIET REPUBLICS[1]

F. LEVITIN[2]

The incidence and mortality from tuberculosis were very high in Tsarist Russia. In 1912 a charity organization entitled "The All Russian League for Combating Tuberculosis" was founded by the Pirogov Society within the confines of which most progressive elements opposing the existing régime tried to render relief to individuals with tuberculosis. Under the control of this League in 1912 there were 43 dispensaries and 18 institutions of the sanatorium type with 307 beds.

The October revolution abolished the social roots of tuberculosis in this country. During the years since the revolution the mortality and incidence rate from tuberculosis have greatly decreased, as much as two and a half times compared with the rates in 1913. The temporary loss of working capacity caused by tuberculosis in the principal extractive industries has decreased three times compared with the rate in 1926. The greatest decrease of tuberculosis incidence has been achieved among industrial workers. Tuberculosis has become of appreciably less frequent occurrence in the remote national republics of U.S.S.R., districts in which prior to the revolution the annual number of tuberculosis victims was very great.

In 1919 during the period of civil war an antituberculosis section was organized in the Commissariat of Public Health. Its task was to plan and carry out antituberculosis measures.

In 1919 and 1920 the first tuberculosis dispensaries were organized. Their experience has formed the basis for all of the work now conducted in dispensaries and other tuberculosis institutions throughout the Soviet Union.

The establishment of tuberculosis sanatoria and summer colonies has proceeded at a high rate. Some of the best apartments in private residences have been allotted for this purpose. The southern coast of the Crimea and the best regions of the Caucasus were converted into health resorts for workers and peasants. The former Tsarist palaces were taken over and organized as sanatoria for workers, peasants and their children. In 1941 there were 15,751 beds available in 208 tuberculosis institutions. In these institutions 12,621 beds were for adults and 3,130 for children.

Besides these hospitals and sanatoria, auxiliary institutions were opened in connection with tuberculosis dispensaries, both for adults and children, such as night and day sanatoria, sanatorium and kindergartens, and dietetic restaurants. In the night sanatoria patients were provided with the necessary treatment and nutrition so that they might acquire good health habits without discontinuing

[1] This report is a transcription of a wireless message sent by Dr. Levitin to the Soviet Embassy in Washington. The transcription was approved by the Embassy.

[2] Administrative Chief, Anti-Tuberculosis Medical Institutions, Peoples Commissariat of Public Health.

some work in their occupation. This type of sanatorium proved satisfactory and therefore such institutions have been opened in all large industrial cities throughout the Soviet Union.

The growth in number of tuberculosis dispensaries can be seen from the following figures. In 1913, there were in Russia only 42 ambulant clinics but not a single permanent dispensary. In 1919 the first of 4 dispensaries was organized and five years later the number had grown to 84. In fifteen years the number had increased to 416. By 1941 there were 1,408 dispensaries functioning, of which 858 were in Russian Socialist Federative Soviet Republic.

The number of permanent and semi-permanent auxiliary tuberculosis institutions is constantly growing. Thus in 1941 the number of hospital beds for tuberculosis patients throughout the U.S.S.R. amounted to 26,390. These hospitals receive tuberculosis patients, both adults and children, and provide treatment for pulmonary tuberculosis and also tuberculosis of the bones. Out of the total number of 26,390 beds there are 5,493 for children. The number of beds for patients with bone and general tuberculosis total 4,281.

Thus it will be noted that, whereas the total number of beds for tuberculosis patients in hospitals and sanatoria throughout Tsarist Russia totalled only 307, the number in Soviet Russia in all of the sanatoria and health resorts totalled 53,523 beds at the beginning of the present war. Of this number 30,857 were allocated to children. It is further noted that of these beds for children 16,000 were available for those with bone and joint tuberculosis.

The tuberculosis dispensary is the main centre for combating tuberculosis having full charge of all medical and prophylactic measures.

In organizing the tuberculosis dispensaries use has been made of experience gained in kindred Western European institutions, mostly the English tuberculosis dispensaries. However the Soviet tuberculosis dispensary may be said to differ essentially from its prototypes elsewhere.

A general network of state medical institutions, the auxiliary institutions connected with antituberculosis dispensaries, the night and day sanatoria, and also medical service in the home offer additional possibilities for prophylactic treatment among the tuberculosis patients. Coöperating with this general network of public health protection the tuberculosis dispensaries obtain from consultations at the polyclinics the names of patients with tuberculosis in the early stages. Such coöperation of the tuberculosis dispensary with the general medical protection service for health protection gives favorable results in treatment and prevents the development of tuberculosis in its more serious stages. On January 1, 1941 there were 2,815 physicians and 4,337 nurses employed in tuberculosis dispensaries through the U.S.S.R.

The personnel of the tuberculosis dispensaries also participates in the establishment of sanitary and hygienic conditions throughout industry. The dispensary physicians and nurses have often been pioneers in this medical work in the factories. Along with general health measures the tuberculosis physicians carry out their specific functions, thus reducing the incidence rate from tuberculosis and preserving the working capacity of tuberculosis patients. Their

reports reveal that tuberculosis patients are organizing to obtain proper nutrition for which huge funds have been allotted by the trade unions. These unions also extend to them labor relief funds.

Examination of workers is carried out in the dispensaries to reveal those in the early stages of pulmonary tuberculosis.

Tuberculosis dispensaries have been organized in Kalinin, Moscow, Leningrad and other places. Invalided persons with tuberculosis have been organized into special artels (workmens associations) where they manufacture wares in wide public demand. Here the method of graduated labor has been applied. It was found that with a reduced working day and proper nutrition, the working capacity of these tuberculosis patients was preserved for a long time.

A majority of these tuberculosis dispensaries have noted the apparent effect of the above plan. In these artels the temporary loss of working capacity has been constantly reduced while the clinical course of the disease has been improved. Some interesting figures in this connection are cited by the Kirov Tuberculosis Dispensary. Due to an improvement in labor conditions the annual number of days of invalidism from tuberculosis was cut in half.

One particularly important task of the tuberculosis dispensaries is the early diagnosis of latent forms of the disease. Increased technical equipment of the tuberculosis dispensaries and the high quality of its personnel, as well as the number of valuable investigations into the pathogenesis and clinical course of the disease, have largely contributed to the results.

For the early diagnosis of tuberculosis use is made of roentgen-fluorography. Roentgen pictures are taken on narrow film. This opens greater possibilities in the objective of registering changes detected in the lungs.

The regulations of the federal republics enable the dispensaries to protect the population from contamination with tuberculosis. For individuals engaged in the food industry there are medical and hygienic institutions and also childrens' institutions, schools, etc. These workers undergo special examinations. All bacillary patients thus detected are being isolated. In the hostels the carriers of bacilli are isolated in special departments. According to regulations disinfection in institutions and at home is obligatory. Persons affected with tuberculosis are allotted additional floor space. Bacillary patients are provided with a separate room.

The most important task of the Soviet tuberculosis dispensary is prophylaxis in tuberculosis foci. It will be seen from the annual reports of tuberculosis institutions that the nurses make about 700,000 visits a year and they succeed in improving hygienic home conditions among persons with tuberculosis.

Among the methods of medical treatment for tuberculosis, sanatorium treatment including surgery is of the widest use. Artificial pneumothorax has become very popular within the last twenty years and is the most effective method of treating pulmonary tuberculosis. Within recent years such methods as thoracoplasty, phrenic evulsion or the use of the cautery and alcoholic injection treatment on both phrenic and intercostal nerves have been widely used. Hygienic treatment in sanatoria has been accessible throughout the Soviet Union to the

working masses and sick people are not required to pay for accommodations in health resorts obtained from the public health service. Besides climatotherapy, collapse therapy is also employed in these health resorts, all of which has greatly improved the results of treatment.

These antituberculosis measures have been developed in close coöperation and with the support of workers and trade unions. Organizations for social relief were organized in connection with tuberculosis dispensaries beginning in 1923. Representatives of factories, trade unions and other organizations have rendered great assistance in the development of the campaign against tuberculosis and in favor of health measures. Three-day campaigns against tuberculosis have proved to be of great significance and have attracted the attention of the working masses to the problem involved in the prevention of tuberculosis.

THE SERIOUSNESS OF MINIMAL PULMONARY TUBERCULOSIS[1]

S. C. STEIN AND HAROLD L. ISRAEL

The outlook for patients with minimal tuberculosis, when contrasted with the outlook for patients with advanced tuberculosis, has appeared so favorable that it has seemed almost sufficient to make an "early" diagnosis to ensure a satisfactory result. This belief has been based largely on reports of the benign course of minimal tuberculosis observed in patients in sanatoria, such as at Trudeau Sanatorium, where a fatality rate of only 2 per cent was noted in patients with minimal disease after six years' observation (1). It is the purpose of this report to point out that sanatorium patients comprise a selected group and that observations on the course of minimal tuberculosis in members of this group are not applicable to the problem in the population at large.

Studies at the Henry Phipps Institute of the course of minimal tuberculosis have shown widely divergent results in different groups. Observation of a group of 16 students, found to have asymptomatic minimal tuberculosis in a survey of a municipal teachers' training college, revealed that 5, or 31.1 per cent, had died within six years (2). Among clinic patients diagnosed as having clinically manifest minimal tuberculosis at the Henry Phipps Institute between 1932 and 1937, fatality rates of 9.1 per cent in whites and 15.0 per cent in Negroes were found after a somewhat shorter average interval of observation (3). Observation of medical students (4) and student nurses (5) with minimal tuberculosis has shown an extremely low fatality rate; in both these groups, however, roentgenological and clinical progression have been frequently noted.

It is obvious that to a considerable extent the differences in course exhibited by sanatorium patients and by clinic patients and professional groups are the result of the social and economic differences among these groups. In addition, however, the prognosis in minimal tuberculosis depends upon whether the lesion is of an acutely progressive type or of a chronic, slowly progressive type. If previous X-ray films are available, it may be possible to determine accurately whether the lesion is of recent origin. In most instances, prior films are not available, and estimates as to the duration and character of the disease must be based on the roentgenological appearance of the lesion or upon the length of illness reported by the patient. Unfortunately, judgments as to the age of a lesion based on roentgenological appearance are frequently in error, and only a small minority of patients with minimal tuberculosis have symptoms. It is because of these difficulties that paradoxically the prognosis is in general better in patients with symptomatic minimal tuberculosis than in those with asymptomatic disease. The very fact that after several months of ill health a lesion has not advanced beyond the minimal stage indicates that the process is a proliferative, slowly progressive one. There can be no such presumption of chronicity in asymptomatic disease: minimal tuberculosis detected in the asymptomatic phase actually represents a cross-section of potentialities. Some of the lesions

[1] From the Henry Phipps Institute of the University of Pennsylvania, Philadelphia.

may be stable, some may be retrogressive, some slowly progressive and some, as in the following case, acutely progressive.

R. D., an Italian female, aged fifteen, was examined in 1934, as an apparently healthy contact of a tuberculous sister. The tuberculin reaction was positive. X-ray examination at the time of the initial visit was negative, as were periodic films made at three to eight month intervals because of recurrent exposure. In December, 1937 the presence of a faint apical infiltration was suspected. A definite patch of flocculent infiltration was visible on reëxamination four months later. Although there were no symptoms or physical signs and although the sedimentation rate was normal, sanatorium treatment was advised, application for admission was made and the patient was instructed to stop work and to rest at home. The patient was reëxamined one month later when her call to the sanatorium was received. There had been a nine pound weight gain, and there were no symptoms, but X-ray examination revealed the development of a cavity 2 cm. in diameter. The patient was given the routine rest treatment at the sanatorium. It was not until four months later that respiratory symptoms developed and positive sputum was obtained. Pneumothorax treatment was refused and the patient died of tuberculosis in April, 1939.

This case is not only an instance of rapidly progressive tuberculosis occurring in the asymptomatic phase, but serves also to point out another factor responsible for the divergent results seen in sanatoria and in clinics. This patient represented to the clinic a fatal termination of minimal tuberculosis; to the sanatorium, however, she represented the fatal end of a case of moderately advanced disease. It is quite the rule for weeks and even months to elapse before admission to a sanitorium is effected. Patients found to have asymptomatic minimal tuberculosis, when examined in a survey or in a clinic, not uncommonly have had progression of disease by the time they are admitted to the sanatorium. Frequently patients with asymptomatic minimal lesions will refuse institutional care until symptoms appear as the result of cavity development.

It appears correct, therefore, to consider those patients who enter sanatoria with minimal lesions as a selected group, not comparable to the total of patients found with minimal tuberculosis in clinics and in surveys. Many patients in the latter group, by constitution or by circumstances, are less well favored in that they may have a greater proportion of acutely progressive lesions, a lesser opportunity for speedy sanatorium admission or a poorer psychological or sociological ability to accept immediate sanatorium care, if such opportunity exists.

The present program of mass X-ray examination is directed principally at those groups in which tuberculosis presents the most serious problem: contacts of known cases, industrial workers, the unemployed. It would be a mistake to base the management of cases of minimal tuberculosis found in such surveys on expectations derived from the course of the disease as observed in sanatorium patients. It would be much more reasonable to base treatment on the course observed in the other groups of the population. Table 1 has been prepared to show the outcome of disease in 66 consecutive patients with minimal tuberculosis, diagnosed at the Henry Phipps Institute between 1937 and 1940, concerning whose status information was available a year after diagnosis. This number

does not include the large group of patients whose lesions were obviously or apparently healed; only those patients whose X-ray shadows appeared to the roentgenologist sufficiently flocculent or extensive to warrant consideration of treatment are included. The lesions were in most instances asymptomatic.

The frequency with which progression, often fatal, occurred is especially significant in view of the relatively short period of observation. As suggested by the case history given above, progression occurred in some cases despite relatively prompt application of therapy. In other cases, progression presumably occurred because of failure to follow the recommendations of the staff conference. In a number of cases, however, progression probably resulted from the failure of the staff conference to advise proper treatment. Although the serious potentialities of asymptomatic minimal tuberculosis have long been recognized and emphasized at the Henry Phipps Institute, inability to distinguish, roentgenologically, fresh from chronic lesions frequently results, especially in older patients, in the recommendation of observation instead of the immediate application of treatment.

TABLE 1

The results of observation of clinic patients with minimal tuberculosis*

	NUMBER OF PATIENTS	DISEASE STABLE OR RETROGRESSIVE	INDETERMINATE RESULT	DISEASE PROGRESSIVE	
				Alive	Dead
White	16	8 (50%)	2 (13%)	5 (31%)	1 (6%)
Negro	50	24 (48%)	2 (4%)	13 (26%)	11 (22%)

* The period of observation ranged from one to five years; the mean duration was 30.8 months.

It is evident that the present vigorous campaign for detection of minimal tuberculosis by roentgen-ray examination of large groups of the population will avail but little if mere observation or only brief periods of treatment are given patients with such lesions. It is necessary that the serious potentialities of asymptomatic minimal tuberculosis be recognized, that adequate sanatorium facilities be provided and that sanatorium physicians realize that the treatment, as shown by Fales and Beaudet (6), must be prolonged and intensive.

SUMMARY

The prognosis in minimal tuberculosis is less benign than is suggested by sanatorium reports. Patients admitted to sanatoria several months after diagnosis or after onset of symptoms, and whose disease is still minimal in extent, as a rule have chronic lesions which respond well to treatment. Fresh lesions which may progress rapidly are frequently encountered among patients whose disease is detected in the asymptomatic phase by clinic or survey examinations. The seriousness of minimal tuberculosis is demonstrated by the occurrence of progression in more than a third of patients with minimal lesions observed at the Henry Phipps Institute.

SUMARIO

En la tuberculosis mínima el pronóstico no es tan benigno como lo harían esperar los informes sanatoriales. Los pacientes que ingresan en el sanatorio a los varios meses de hacerse el diagnóstico o de iniciarse los síntomas, y cuya enfermedad es todavía de extensión mínima, revelan por lo general lesiones crónicas que reaccionan bien al tratamiento. Los enfermos en que el examen clínico o sistemático pone de manifiesto la dolencia, revelan con frecuencia lesiones recientes que pueden evolucionar rápidamente. El avance de la enfermedad en más de la tercera parte de los enfermos con lesiones mínimas atendidos en el Instituto Henry Phipps, demuestra la gravedad de la tuberculosis mínima.

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UNRECOGNIZED TUBERCULOSIS IN A GENERAL HOSPITAL[1]

JASON E. FARBER AND WILLIAM T. CLARK

The relatively high incidence of tuberculosis among hospital employees and student nurses has for some time been recognized as a problem of considerable importance. Our experience at the Meyer Memorial Hospital has not differed from studies (1, 2, 3, 4, 5) which report a high infection and morbidity rate among these persons. For several years tuberculous patients admitted to the Meyer Memorial Hospital have been isolated on tuberculosis pavilions where the rigid technique, commonly used in acute communicable diseases, is carried out. Undiagnosed chest cases and those suspected of having tuberculosis are isolated on a similar ward governed by similar measures of "contagion technique." In spite of these precautions the incidence of tuberculosis among student nurses[2] and other young hospital employees has remained high. Only 25 to 30 per cent of the student nurses are tuberculin-positive at the beginning of their training period whereas approximately 60 per cent are found to be positive before they have worked on the tuberculosis service, one year later. One of the factors responsible for this may be the presence of undiagnosed cases of tuberculosis on the general wards. Each year an appreciable number of patients admitted to the various wards of the hospital for nontuberculous conditions are later found to have significant reinfection type tuberculosis.

In the recent literature there have been several important contributions to the subject of unrecognized tuberculosis in general hospitals (6, 7, 8). Plunkett and Mikol (6) found that in a series of 4,853 consecutive nontuberculous admissions to a group of general hospitals there were 128 (2.6 per cent) cases of pulmonary tuberculosis. Of these, 51 (1.1 per cent of the total) showed clinically significant tuberculosis, as determined by the X-ray examination. To show more clearly the magnitude of the problem, Plunkett and Mikol estimated that there probably were more than 40,000 unrecognized cases of pulmonary tuberculosis hospitalized in the United States in the year 1937.

The present study is an analysis of 100 patients, consecutively admitted to the Meyer Memorial Hospital[3] with diagnoses other than tuberculosis, who were later found to have clinically significant reinfection type tuberculosis. These patients were admitted over an interval of three years (January, 1939 to January, 1942), during which period there were roughly 30,000 admissions to the hospital. These 100 cases, therefore, comprise about 0.3 per cent of the total number of hospital admissions for that period. In the light of Plunkett's study (6) one might speculate that these 100 cases represent approximately one-fourth of an expected number of such cases. The other three-fourths, it may be assumed,

[1] From the Edward J. Meyer Memorial Hospital and the University of Buffalo School of Medicine, Buffalo, New York.

[2] Data regarding morbidity among this group will be reported in a subsequent communication.

[3] Bed capacity 1,131.

remained on the general wards and were eventually discharged without ever having been diagnosed.

In the present study the following data have been analyzed: age, race, extent of disease, sputum findings, number of days before transfer to the tuberculosis service, hospital service to which patient was admitted, admission diagnoses, clinical symptoms and signs and X-ray diagnosis. These various factors will be considered separately.

Sex, age and race: There were 79 male and 21 female patients. Of these, 85 were white, 13 colored, one American Indian and one Chinese. The ages of the male patients ranged from sixteen to eighty-three years, the median age being fifty-four. The ages of the female patients ranged from twenty to seventy-two, the median age being thirty-one.

Type and extent of disease:[4] There were 95 pulmonary cases whose findings are summarized in table 1.

TABLE 1

Type and extent of disease

Pulmonary—Minimal	14
Pulmonary—Moderately advanced	25
Pulmonary—Far advanced	56
Tuberculous lymphadenitis	4
Tuberculous pleurisy with effusion*	1
Acute miliary tuberculosis	3
Tuberculosis of kidney	1
Bone tuberculosis*	2

* Also had pulmonary lesions.

The instances of combined pulmonary and extrapulmonary tuberculosis have been included under both headings. The miliary cases have been classified as advanced pulmonary tuberculosis.[4]

Hospital services: It is of interest that these patients were found on practically every type of hospital service. As shown in table 2, more than half of the patients were discovered on medical services. In all probability this is due to the fact that more of the hospital admissions are medical rather than surgical.

Admission diagnoses: A wide variety of conditions were represented in the original admission diagnoses (table 3). It should be stated, however, that in addition to the unrecognized tuberculosis more than one-half of the patients did have the disease which was recorded at the time of admission. The cases listed as "cardiovascular disease" were diagnosed as cardiac decompensation, rheumatic endocarditis and coronary sclerosis. The relatively frequent occurrence of tuberculosis among mental patients is not unexpected (9).

Number of days before transfer: As long as there is unrecognized tuberculosis on general hospital wards, there is a constant danger to hospital employees, fellow patients and hospital visitors. The number of days before transfer to

[4] Diagnostic Standards, National Tuberculosis Association, 1940 Edition.

the tuberculosis wards ranged from one to one hundred and forty-six days, the median number of days being eight. There was a total of 1,497 hospital days of exposure before transfer to the tuberculosis service.

TABLE 2

Type of hospital service

General medicine	52
General surgery	9
Orthopedic surgery	4
Proctology	4
Urology	4
Ophthalmology	1
Obstetrics, gynecology	5
Dental surgery	2
Neurology, alcoholism, drug addiction	10
Psychiatry	5
Dermatology, syphilology	4
Total	100

TABLE 3

*Admission diagnoses**

Dermatitis	2	Ruptured appendix	1
Arthritis	6	Lumbo-sacral strain	1
Cardiovascular disease	7	Neurological study	3
Cord bladder	1	Mass in abdomen	1
Retained placenta	1	Diabetes mellitus	3
Drug addiction	1	Pulmonary fibrosis and emphysema	4
Alcoholism	5	Carcinoma of lung	1
Hodgkins disease	2	Asthma	6
Pleural effusion	2	Stasis ulcer	1
Cerebral accident	2	Peptic ulcer	2
Undetermined oedema	1	Nephritis	1
Mental observation	5	Pelvic cellulitis	1
Tabes dorsalis	1	Malnutrition	2
Ectopic pregnancy	1	Rectal fistula or abscess	4
Cataract	1	Parkinson's disease	1
Undetermined medical	6	Chronic sinusitis	1
Cervical adenitis	3	Hernia	3
Ulcer right heel	1	Chronic appendicitis	1
Fracture right hip	1	Thrombophlebitis of jugular vein	1
Gastro intestinal malignancy	4	Cerebral lues	1
Alveolar abscesses	2	Hypertension	1
Pregnancy	2	Acute urinary retention	1
Congenital lues	1	Lung abscess (?)	1

* Figures denote number of cases with stated diagnosis.

Clinical data: From an epidemiological standpoint the important symptoms of pulmonary tuberculosis are cough and expectoration, since the greatest danger originates with the tuberculous patient who coughs and expectorates. In the present series, 71 patients had a definite and productive cough. In 5 instances a

frank haemoptysis focussed attention on the pulmonary lesion. Eight patients complained of pain in the chest and 4 had an unexplained fever. Of particular importance is the fact that abnormal physical signs in the chest led to a presumptive diagnosis of tuberculosis in only 16 instances.

X-ray diagnosis and sputum status: An X-ray film of the chest was taken on each patient at varying intervals after admission, usually just prior to transfer of the patient to the tuberculosis service. Classification of the lesions, as mentioned previously, conforms to the Diagnostic Standards of the National Tuberculosis Association. Clinically significant reinfection type pulmonary tuberculosis was found in 95 cases. The remaining 5 cases in the series had only extrapulmonary tuberculosis.

Sputum was available for examination in 95 instances. It was not obtained in 2 psychiatric patients and in the 3 patients with miliary tuberculosis. Five of the extrapulmonary cases had negative sputum but 2 of them were discharging bacilliferous exudate from sinuses and one had a positive urine. Of the remaining 90 pulmonary cases, 68 (76 per cent) were positive.

DISCUSSION

This study is an attempt to evaluate the danger which is imposed upon hospital personnel by unrecognized cases of tuberculosis. The physical arrangement of the ward services and the student nurses' program at the Meyer Memorial Hospital have permitted, in a limited sense, a clinical experiment to be performed. As previously mentioned, all known cases of tuberculosis are isolated on the wards of a tuberculosis service and all cases suspected of having tuberculosis are isolated on a ward where "contagion technique" is employed. In addition, student nurses are not permitted to work on these wards until after their first year of training, although they do work on the various other hospital wards. Yet our records show that during the first year of training approximately 30 to 35 per cent of the student nurses become infected with tubercle bacilli.[5] Soper and Amberson (10) noted that among student nurses "tuberculin studies almost without exception indicate an accretion of infection year by year quite out of proportion to the general population." Our findings suggest that an important source of this tuberculous infection is in the hospital and can be attributed to unsuspected tuberculosis on the general wards.

A study has been made of 100 patients admitted with nontuberculous diagnoses who were later found to have clinically significant tuberculosis. It is these patients who constitute an important source of infection prior to their discovery, so that any information as to why the diagnosis was missed on admission or how to recognize these cases sooner has practical value. It must be mentioned again that the 100 cases comprising the study represent only those that were discovered and that in all probability there were many others with tuberculosis on the general wards who were not diagnosed either because suspicious symptoms were absent or not recognized or because their chests were not X-rayed.

[5] Dr. Donald McKay, Visiting Physician, Tuberculosis Service, kindly furnished the data on the tuberculin tests of the nurses.

While 79 per cent of the patients in the present series were males, it is of greater interest that the median age of the men was fifty-four, and that this was twenty-three years higher than that of the women. This agrees, in general, with data for large groups of the population (11) which show that the peak of tuberculosis mortality in white males is in the age group forty-five to sixty-four years, and in white females in the age group twenty to twenty-four.

Of further interest is the fact that 81 per cent of the patients had advanced pulmonary tuberculosis at the time of diagnosis. From the public health point of view a positive sputum is of major importance. In the series, there were 68 patients with positive sputum. Three others were discharging tubercle bacilli from extrapulmonary foci. Sputum or other exudate was not obtained for examination in 5 instances. Seventy-one of the patients had a productive cough. As a matter of fact, the majority of patients were suspected of having tuberculosis because of cough and expectoration. It was because of the presence of these symptoms that X-ray films of the chest were taken. A smaller number of the group had haemoptysis, unexplained fever and pain in the chest, symptoms that lead to a search for the disease. In only 16 patients were abnormal physical signs in the chest directly responsible for a tentative diagnosis of tuberculosis. However, it should be stated that, whereas the majority of the patients did have abnormal physical signs in the chest, the signs, *per se*, were evidently not the immediate reason for suspecting tuberculosis. All patients had an X-ray film of the chest which confirmed the diagnosis in all the pulmonary cases.

A word may be said in regard to the manifold diagnoses at the time of admission. Tuberculous patients commonly suffer from associated pathological conditions, for tuberculosis is antagonistic to few disease processes. Generally speaking, the older the group of tuberculous patients the more frequent the associated nontuberculous diseases. Experience reveals that the incidence of diagnosis of these nontuberculous conditions is directly proportional to the thoroughness of examination and to the clinical acuity of the physician. On the other hand, some of the patients had only tuberculosis and did not have the disease recorded at the time of admission. This illustrates the well known fact that tuberculosis may disguise itself in various ways.

The findings of the present study suggest that every hospital patient who produces sputum, regardless of his diagnosis, should at least have his sputum examined for tubercle bacilli. A tuberculosis-conscious medical staff will order more X-ray films of the chest, especially among the groups of patients in whom the disease is more prevalent. Edwards' (12) studies have pointed to the high incidence of tuberculosis in certain underpriviledged groups. Certainly, if all patients admitted to general hospitals were X-rayed much tuberculosis would be discovered. This procedure should become routine when fluorograms are used in admission departments of all hospitals. But until such a time there remains the hazard of exposure from the hidden cases of tuberculosis on the wards of general hospitals.

SUMMARY AND CONCLUSIONS

An analysis has been made of 100 patients admitted to a general hospital with nontuberculous diseases, who were later found to have tuberculosis. These

unrecognized cases of tuberculosis create a significant public health problem, for they constitute a major hazard to hospital personnel and patients. Most of the cases in the present series were suspected of having tuberculosis on the basis of symptoms rather than physical signs. At the time of diagnosis, 81 per cent of these patients had advanced tuberculosis. There were 1,497 hospital days of exposure before transfer to the tuberculosis wards and the median number of days before transfer was eight. It is recommended that all adult admissions to general hospitals have an X-ray examination of the chest. The study emphasizes the danger of unrecognized tuberculosis in a general hospital.

SUMARIO Y CONCLUSIONES

Analízanse 100 enfermos recibidos en un hospital general por afecciones no tuberculosas y que luego se descubrió que tenían tuberculosis. Esos casos de tuberculosis desapercibida crean un significativo problema sanitario, pues constituyen un riesgo mayor para el personal y los enfermos del hospital. En la mayor parte de los casos de la serie estudiada se sospechó tuberculosis tomando por base los síntomas más bien que los signos físicos. Al hacerse el diagnóstico, 81% de ellos revelaron tuberculosis avanzada, habiendo habido 1,497 días de hospitalización, promediando ocho días antes del traslado a la sala de tuberculosos. Recomiéndase que en todo ingreso de adultos en los hospitales generales se haga un examen roentgenográfico del tórax. Este estudio pone de manifiesto el peligro que entraña la tuberculosis no reconocida en un hospital general.

We are indebted to Dr. Edward X. Mikol, Albany, New York, for friendly advice.

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THE HEART IN PULMONARY TUBERCULOSIS[1]

Studies of the Auricular Complex in the Electrocardiogram

THEODORE T. FOX AND HERMAN S. KREMER

The subject of *cor pulmonale* has been alloted considerable space in the recent literature. The acute form is now recognizable as a definite clinical entity with a more or less characteristic electrocardiographic pattern obtained during and shortly after an attack (1). The recognition of chronic *cor pulmonale* is still difficult in most cases until symptoms of congestive failure supervene because the symptoms of the underlying pulmonary insufficiency are frequently similar to those due to cardiac embarrassment, and the signs in most cases are difficult to interpret. Both acoustic and fluoroscopic evidence of pulmonary hypertension may be camouflaged by structural distortion of the mediastinum and, conversely, parenchymatous and pleuritic abnormalities may produce false evidence both acoustically and fluoroscopically. Even when congestive failure sets in, the diagnostic difficulties are not completely removed. Distended neck veins, a sign of right heart failure, are not infrequently due to superior mediastinal adhesions, and a large liver and peripheral oedema may be an expression of amyloidosis or nutritional hypoproteinaemia complicating advanced pulmonary disease.

Notwithstanding the difficulties, the recognition of the existence of depleted or strained cardiac reserve in cases of pulmonary disease is obviously of great practical importance. It is particularly so when one is called upon to form an opinion on contraindication to surgical interference, particularly thoracoplasty.

One naturally turns to electrocardiography for further assistance in the diagnosis of right heart strain; and for many years the finding of right axis deviation was considered an important criterion in the syndrome of *cor pulmonale*. However, the validity of this criterion is not absolute. The finding of right axis deviation with heart enlargement and clear pulmonary fields is undoubtedly of significance. But in cases with gross pulmonary disease, this factor, like those mentioned above, is of questionable validity, as directional changes of the QRS-complex may be merely an expression of mediastinal torsion and displacement (2, 3). This fact needs repeated emphasis, since most authors in discussing right axis deviation as the electrocardiographic criterion of *cor pulmonale* fail to mention mediastinal displacement as a factor in the differential diagnosis (4, 5). Evidence will be presented later to show that deflectional changes occur more often when the heart is displaced into the left chest than when it is displaced into the right. Obviously this fact will tend to increase the number of cases with right axis deviation in any group studied, and lead to an erroneous conclusion as to the incidence of chronic *cor pulmonale*. On the other hand, a certain number of cases with right heart hypertrophy and mediastinal displacement to the right will have no axis deviation or possibly even a marked left

[1] From the Cardiac Service, Sea View Hospital, Staten Island, New York.

axis deviation. Thus the axis deviation, in cases of gross pulmonary disease, ceases to be of diagnostic significance.

The typical electrocardiographic picture of chronic *cor pulmonale* has received an additional criterion in recent years, namely the abnormal auricular complex. This complex, normally a rounded arch-like wave 1–2.5 mm. high and about 0.10 seconds wide, supposedly assumes a taller appearance, particularly in leads II and III, in the presence of right auricular distention or hypertrophy. The abnormality of the auricular wave may also express itself in a diphasic direction or notching (2). It is thought by some observers (6) that one would be less apt to overlook the existence of right heart strain, if the abnormalities in the P-wave would be given greater consideration.

In our clinical experience at Sea View Hospital we failed to notice a definite relationship between the abnormal auricular complex in the electrocardiogram and the evidence suggestive of pulmonary hypertension. Other factors were suspected to play a rôle in the structural changes of the P-wave. It was felt, therefore, that this subject needs further study.

It is the purpose of this report to correlate the occurrence of abnormal P-waves in the electrocardiogram with clinical, postmortem and experimental observations, and to isolate, if possible, the main factors in the mechanism of these abnormalities.

PROCEDURE AND RESULTS

CLINICAL

Statistical: The electrocardiographic tracings of 804 patients with pulmonary tuberculosis taken at Sea View Hospital between January and June, 1941 were reviewed with particular reference to the structural changes in the P-wave; 76 tracings presented a P-1 with an amplitude less than 0.5 mm. with no abnormality in P-2 or P-3. Out of this group, 51 showed no axis deviation, 8 showed right axis deviation and 17 left axis deviation. No cases were found with low P-2 or P-3 which did not show inversion or notching of P-1. The significance of a low P-1 as the sole abnormality cannot be evaluated with certainty, but it is quite possible, in view of the result presented in the experimental section of this paper, that it may be indicative of mediastinal displacement.

There were 69 cases showing abnormal P-waves, the abnormality consisting of notching, spiking, widening, inversion or diphasic deflection. These changes occurred in lead-I alone in 5 cases, in lead-II alone in 10 cases, in lead-III alone in no case. Associated changes in leads-I and -II occurred in 9 cases, in leads-I and -III in 2 cases, in leads-II and -III in 6 cases, in all the standard leads in 37 cases. Of these, in 26 cases, a low amplitude was the only abnormality in P-1; in 11, other abnormalities in P-1 were present (8 showed an inverted or diphasic P-1, 3 showed notching of P-1).

Inversion of P-1 was observed in 11 cases. In no case was the change observed without accompanying changes in the other standard leads. It was seen once in association with an abnormal P-3, and once with an abnormal P-2. In 9 cases inversion of P-1 was seen in association with abnormal P-2 and P-3.

Reference to the clinical status of the cases in question revealed the following facts: of the 5 cases with changes in P-1 alone, one, a case with a diphasic P-1 was associated with a right pneumothorax; in another case a diphasic P-1 was associated with a bilateral pneumothorax, the right being greater than the left; the other 3 cases showed notching of P-1 and were not associated with pneumothorax. Inversion of P-1 was associated with right pneumothorax in 8 out of 11 cases; the 3 remaining cases were: (*1*), a case with bilateral pneumothorax, the right being greater than the left; (*2*), a case of bilateral tuberculosis with roentgenographic evidence of displacement of the mediastinum into the left chest; and (*3*) a case with bilateral tuberculosis, more marked on the right side.

Of the 10 cases with abnormalities of P-2 alone, one case showed merely widening of P-2; and 9 cases showed notching and spiking. Of these, 4 had unilateral or bilateral tuberculosis with emphysema; 2 had a right pneumothorax; 2 had bilateral tuberculosis; one had right upper lobe tuberculosis. In this group P-1 was low in 2 cases and normal in 7 cases.

Of the 43 cases with abnormalities of the P-wave in leads-II and -III, with or without associated abnormalities in P-1, 2 had notched P-2 with low or diphasic P-3 and clinically presented extensive bilateral tuberculosis without emphysema in one case, and right pneumothorax in the second case; 3 cases had notching or spiking in all 3 leads and these had intrinsic heart involvement in addition to their pulmonary disease. One case had rheumatic heart disease, one had first-stage heart block (cause unknown), and one case had paroxysmal auricular fibrillation. Of the remaining 38 cases, 16 were cases with bilateral tuberculosis and emphysema, 10 had right pneumothorax, one had bilateral pneumothorax and 11 cases had bilateral tuberculosis. The P-1 in this group was normal in 5 cases, inverted in 7 cases and low in 26 cases. Of the 26 cases with low P-1 and notching or spiking of P-2 and P-3, in 14 (approximately 50 per cent) emphysema was an associated clinical and radiographic finding. The incidence of emphysema in the remaining 43 cases was approximately 25 per cent (10 cases).

Of the 9 cases with P changes confined to leads-I and -II, 5 cases had organic heart disease (4 arteriosclerotic and one rheumatic). One case was of a patient sixty-three years old who may well have had arteriosclerotic heart disease. The other 3 cases had right pneumothorax with low, diphasic or inverted P-1 and notched or low P-2.

Emphysema: In view of the suggestive correlation between emphysema and the P-wave changes in the standard leads, 15 cases of emphysema, sufficiently severe to receive pneumoperitoneum for the relief of dyspnoea, were studied electrocardiographically with particular reference to the form of the P-wave. They all had a variable degree of either exudative or productive tuberculosis. Of the 15 cases, only 2 had right axis deviation, 3 had left axis deviation and 10 had no axis deviation. P-1 was low in 11 cases, variable in amplitude and form in one case and normal in 3 cases. P-2 was notched, spiked or high in 11 cases and normal in 4 cases. P-3 was likewise notched, spiked or high in 11 cases and normal in 4 cases. P changes in all three standard leads were seen in 8 cases.

P-1 in this group was low; changes in leads-II and -III were present in 2 cases. There were no cases with changes confined to leads-I and -II only. There were no cases with P-3 changes alone. Low P-1 without changes in P-2 and P-3 were seen in 3 cases. In only one case was P-2 the sole abnormality; 10 cases had changes in leads-II and -III, an incidence of 67 per cent. It is noteworthy that the amplitude of the P-wave was 3 mm. or over in only 2 of the 15 cases studied.

NECROPSY MATERIAL

Thirty-one cases of right ventricular hypertrophy without hypertrophy of the left ventricle were found among 366 unselected postmortem records extending over a period of three years, 1938 to 1941, an incidence of 8.5 per cent; 15 of these cases had electrocardiographic tracings taken. The known duration of pulmonary tuberculosis in 9 cases of this particular group with electrocardiographic tracings was three years or less. The maximum known duration of the pulmonary disease was seven years. Seven cases were fifty years and older. The youngest case was seventeen years old. Clinical emphysema was stated to have been present in 6 cases, 4 of which had in addition pulmonary tuberculosis and one had silicosis. The other 9 cases of right sided hypertrophy were associated with the following conditions: silicosis, one case; thoracoplasty, two cases; tuberculosis with histological emphysema, six cases. Histological emphysema (around a tuberculous focus) is a frequent finding in pulmonary tuberculosis and was noted in 77 of 100 consecutive autopsy protocols. This is practically a constant accompaniment of productive or healing changes in any but the most acute cases of tuberculosis.

The electrocardiographic findings in the necropsy group were as follows: right axis deviation was seen only in one case; 2 cases showed a tendency to right axis deviation; none had left axis deviation; no axis deviation was seen in 12 cases. A low P-1 as the sole abnormality was seen in one case; spiking of P-1 and P-2, in one case; a low P-1 and notched P-2, in one case; a spiked or notched P-2 as a sole abnormality occurred in 4 cases; simultaneous changes in P-2 and P-3 took place in 2 cases; changes in all standard leads, consisting of a low P-1 and notched P-2 and P-3 (cases with clinical emphysema) occurred in 3 cases (20 per cent); 3 cases had normal P-waves in the standard leads (20 per cent). The total number of cases with P-2 and P-3 changes were 5, an incidence of 33 per cent. It is of interest to note that of the 6 cases with clinical emphysema, 3 showed a low P-1 and notched or spiked P-2 and P-3; P-2 changes were present in 4 of the 6 cases. The predominant feature in the material studied apparently was an abnormal P-2 which occurred in 11 cases. Thus, the necropsy material does not support the conclusions one could draw from the analysis of the clinical material, namely: that a low P-1, in association with a notched or high P-2 and P-3, constitutes an electrocardiographic pattern indicative of right heart strain.

Reference to the time interval between the recorded electrocardiograms and the date of death revealed the following facts: in 5 cases the time interval was days; in this group one had normal P-waves in all standard leads and 2 had a

low P-1 as the sole abnormality. In 4 cases the interval was from 3 to 10 months: 1 case had normal P-waves in all standard leads and one had a low P-1 as the sole abnormality. In 6 cases the interval was from one to three years (one and one-half years in 4 cases); all had abnormal P-waves. If the abnormal P-wave in this series would be definitely indicative of right heart strain one would hardly expect to find an increasing number of normal auricular complexes as death approaches. The fact that the majority of cases in the necropsy series

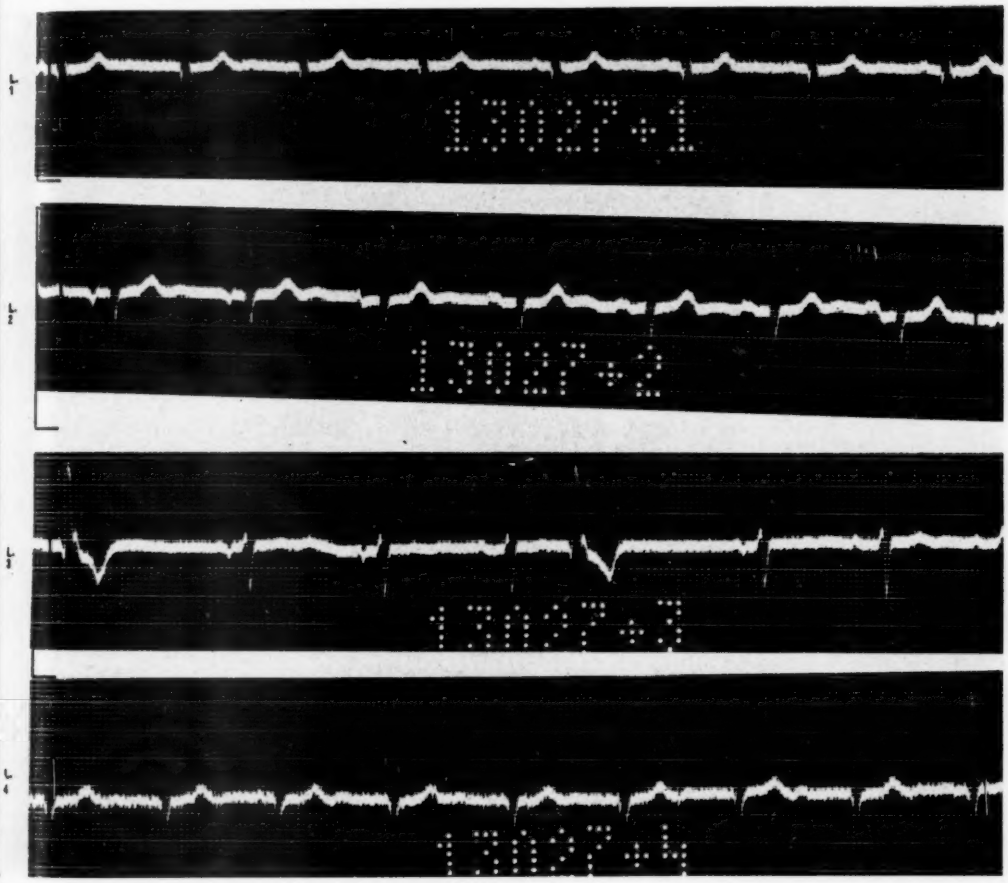

FIG. 1. *The effect of respiration(?) on the form of the P-wave.* Note the extreme variability in the configuration of the auricular complex, particularly in lead-II. Note the changing length of the "P-R interval."

had some P-wave abnormality in the electrocardiogram is probably due to the distortional pulmonary disease found at postmortem examination (*vide infra*).

EXPERIMENTAL

(*a*) Since the P-wave is structurally similar to a miniature QRS-complex, it is reasonable to assume that it too should show deflectional changes with medias-

tinal torsion and displacement. Such changes should, and do, also occur with respiration. Occasionally, one sees a tracing where not only does the form of the P-wave change with mediastinal shift, but the *measurable P-R interval* varies in length. Figure 1 is an electrocardiographic tracing of a man sixty-nine years old, with long standing pulmonary tuberculosis, involving grossly the right upper lung field and causing displacement of the upper mediastinum to the right (figure 2); the heart is not enlarged. He had no symptoms of cardiovascular distress. The electrocardiographic tracing presents a great deal of variability in the form of the P-wave in all standard leads, but particularly interesting are the changes in lead-II, where an inverted P-wave alternates with one that is diphasic and

FIG. 2. *X-ray film of chest of patient whose electrocardiographic tracing is depicted in figure 1.* Note the displacement of the upper mediastinum to the right. Fluoroscopy revealed no enlargement of the heart.

then assumes a wide and notched appearance. The P-R interval varies from 0.16 seconds to 0.21 seconds. This lability of the P-wave associated with mediastinal displacement suggests an explanation of a not infrequent finding of "first stage A-V block" in cases of pulmonary tuberculosis where no rheumatic fever or coronary sclerosis is suspected. This observation has been previously recorded by Pastore (7) in the young, but apparently also occurs in the old. Vagal tone, which is increased at both age extremes, as a component in the mechanism of the "A-V changes" described, cannot be ruled out completely.

In order to see the effect of mediastinal shift on the form of the P-wave, 10 cases with P-1 changes were selected and positional studies done (table 1). Some of the tracings selected had also abnormal P-waves in the second and third leads. Tracings were taken in the supine, right lateral and left lateral positions. The results obtained were as follows: 6 cases showed some deflectional changes

TABLE 1

Positional changes

NAME	CONTROL EGG (SITTING)	RIGHT LATERAL	SUPINE	LEFT LATERAL
J. W.	P-1 Notched	P-1 Notched	P-1 Notched	P-1 Inverted
	P-2 Notched	P-2 Spiked and notched	P-2 Notched, less spiked	P-2 Flat
	P-3 Notched	P-3 Spiked and notched	P-3 Spiked and notched	P-3 Inverted
	Tendency to RAD	Tendency to RAD	Axis same	Axis same
L. G.	P-1 Variable, diphasic and upright	P-1 Normal	P-1 Normal	P-1 Low
	No AD	No AD	Tendency to LAD	No AD
M. M.	P-1 Inverted	P-1 Low	P-1 Flat	P-1 Inverted
	P-2 Normal	P-2 Notched	P-2 Notched	P-2 Spiked
	P-3 Normal	P-3 Notched	P-3 Notched	P-3 Spiked
	Tendency to RAD	Tendency to RAD	No AD	RAD
J. M.	P-1 Diphasic	P-1 Diphasic	P-1 Upright and diphasic	P-1 Normal
	P-2 Diphasic	P-2, 3 Normal	P-2, 3 Normal	P-2, 3 Normal
	No AD	No AD	No AD	No AD
L. O.	P-1 Variable, negative, diphasic and positive	P-1 Isoelectric	P-1 Isoelectric	P-1 Isoelectric
		P-2 2 mm.	P-2 1 mm.	P-2 1 mm.
		P-3 2 mm.	P-3 1 mm.	P-3 1 mm.
		No AD	Tendency to RAD	Tendency to RAD
L. T.	P-1 Inverted	P-1 Variable, normal and low	P-1 Normal	P-1 Inverted
	P-2 Spiked	P-2 Normal	P-2 Normal	P-2 Normal
	P-3 Notched	P-3 Normal	P-3 Normal	P-3 Normal
	RAD	RAD	RAD	RAD (more marked)
J. D.	P-1 Normal	P-1 Normal	P-1 Normal	P-1 Low
	P-2 Inverted	P-2 Normal	P-2 Normal	P-2 Low
	P-3 Inverted	P-3 Inverted	P-3 Diphasic	P-3 Inverted
	No AD	No AD	No AD	Small S-1

TABLE 1 (*Concluded*)

NAME	CONTROL EGG (SITTING)	RIGHT LATERAL	SUPINE	LEFT LATERAL
D. H.	P-1 Inverted and diphasic	P-1 Isoelectric	P-1 Variable: isoelectric, notched and inverted	P-1 Isoelectric
	P-2 Normal and spiked	P-2 Normal and spiked	P-2 Normal and spiked	P-2 Normal and spiked
	P-3 Normal and spiked	P-3 Normal and spiked	P-3 Normal and spiked	P-3 Normal and spiked
	RAD	RAD	RAD	RAD
J. D.	P-1 Inverted	P-1 Normal	P-1 Low	P-1 Inverted
	P-2 Spiked	P-2 Spiked	P-2 Spiked	P-2 Spiked
	P-3 Spiked	P-3 Spiked	P-3 Spiked	P-3 Spiked
	No AD	No AD	No AD	QRS-1, w-shaped and low
S. N.	P-1 Inverted	P-1 Diphasic	P-1 Bifid	P-1 Inverted and diphasic
	P-2 Spiked	P-2 Normal	P-2 Normal	P-2 Normal
	P-3 Spiked	P-3 Normal	P-3 Normal	P-3 Normal
	RAD	RAD	RAD	RAD

in the QRS-complex; 5 cases showed right axis deviation or a tendency to a right axis deviation in the left lateral position; in the supine position no axis deviation was observed in one case with a tendency to right axis deviation in the control (sitting position); a tendency to left axis deviation was observed in another case with a control showing no axis deviation; there were no deflectional changes in the remaining cases in this position. The tracings taken in the right lateral position did not differ at all from the control tracings in the direction of the QRS-complex. This type of QRS deflectional response to mediastinal shift was observed by others (8). Changes in the form of the auricular complex occurred in our series in all positions. They occurred in 9 out of the 10 cases in lead-I, 4 cases showed changes in lead-II; and 4 cases in lead-III. No case was free from positional changes in the form of the P-wave. It may be worthy of note that all but 2 cases had a right pneumothorax.

The type of change in the form of the auricular complex taking place is exemplified in figure 3. A notched P-1 in right lateral position becomes inverted when the patient is in the left lateral position; a tall notched P-2 becomes low, a notched P-3 becomes inverted.

It is apparent from this experiment that the P-wave is very labile and subject to change in contour with mediastinal shift more often than the QRS-complex.

(*b*) Figure 4 presents serial electrocardiographic changes of a patient who

suddenly developed evidence of right heart failure, severe and progressive. The patient received an unknown amount of digitalis for three days prior to admission to Sea View Hospital. On admission, digitalis was discontinued by the resident because the electrocardiogram presented a first stage A-V block. Coincidental

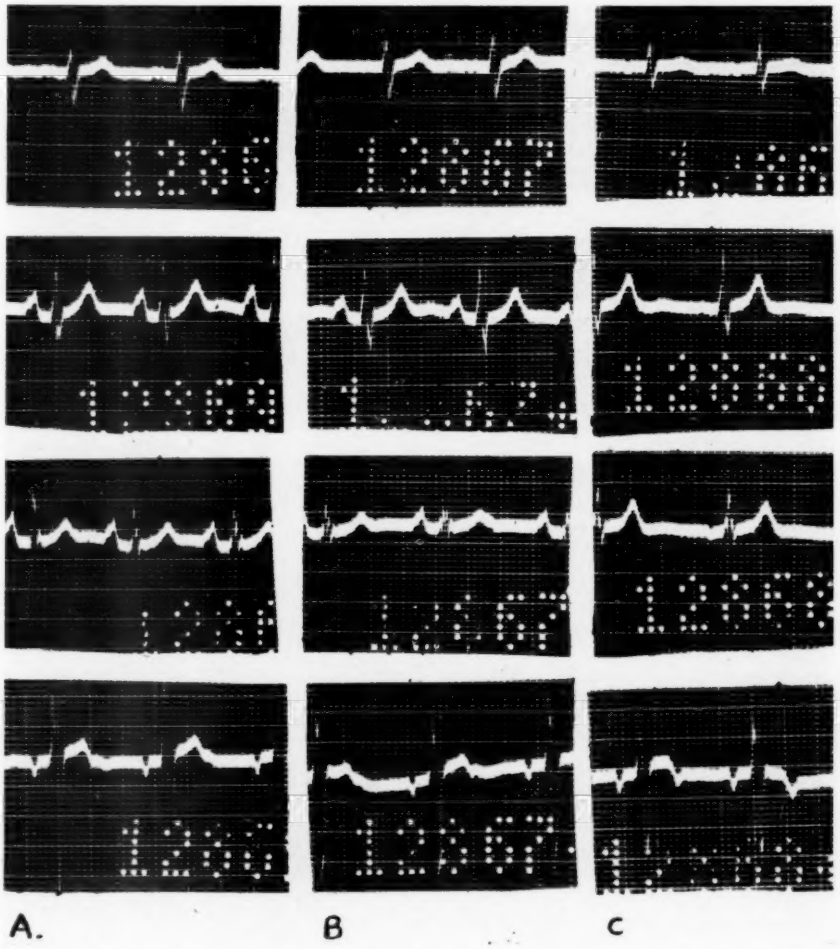

FIG. 3. *The effect of change of position on the form of the P-wave.* A. Patient in the right lateral position. Note bifid P-1, tall and notched P-2 and P-3.

B. Patient in supine position. Note slight diminution in the amplitude of P-2.

C. Patient in the left lateral position. Note inversion of P-1, low P-2 and inversion of P-3. No changes occurred in P-4.

with the increase in congestive failure, P-2 and P-3 increased in size. It was not unreasonable to assume that the change in the P-wave might be due to right auricular distention.

On the basis of this observation, 10 cases with no pulmonary disease, presenting marked evidences of right heart failure, enlarged livers and engorged jugular

veins, were selected. After control tracings were obtained (limb leads only), sufficient pressure was exerted over the enlarged liver to cause pronounced engorgement of the neck veins. The visible veins were frequently estimated to be double their volume and veins invisible prior to pressure, became very prominent. Eight cases had a normal rhythm and normal P-waves. No change in size or shape of the P-wave was induced by the procedure. There were 2 cases of auricular fibrillation. In one of them, the diastolic interval, isoelectric in

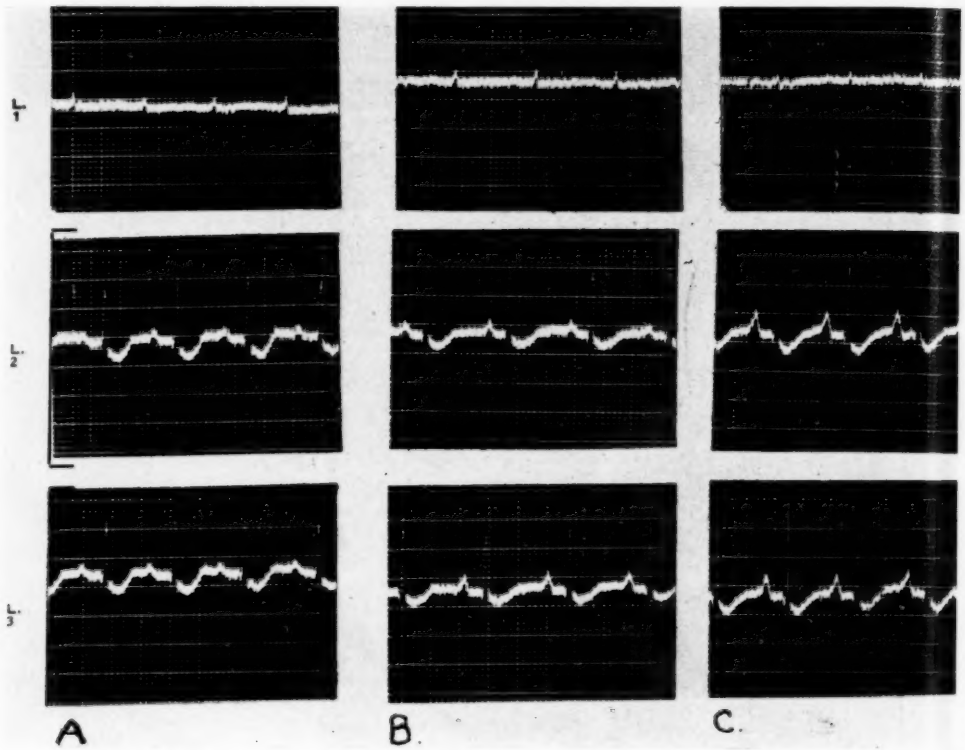

FIG. 4. *The effect of congestive failure(?) on the form of the P-wave.* A. Electrocardiogram taken on May 27, 1941.
B. Electrocardiogram taken on May 28, 1941.
C. Electrocardiogram taken on May 31, 1941.
The patient died the following day.

the control, showed regular F-waves with pressure on the liver. Admittedly, this is a crude experiment. It does not reproduce the physiological set-up of failure, and lacks particularly in the element of time. The duration of the auricular distension in the experiment is not comparable with that in the case cited. The experiment suggests, however, that transient overfilling of the right auricle in itself does not produce changes in the P-wave. The possibility that more prolonged distension of the auricle might be a factor in producing P-wave changes is of course not excluded.

(*c*) The form assumed by the P-wave as a result of mediastinal displacement is not predictable. Instead of becoming taller, notched or isoelectric, it may occasionally become wider, with little or no modification of its amplitude. The spread of the P-wave may so measurably affect the P-R interval as to make it

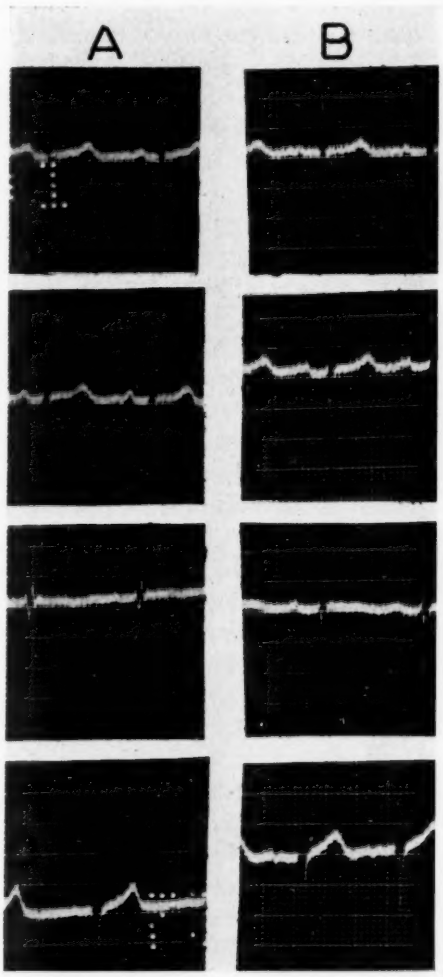

FIG. 5. *The effect of mediastinal displacement on the measurable P-R interval.* A. Control tracing.

B. Tracing taken immediately after 300 cc. of air was instilled into the right pleural cavity. Note the notching of P-2, and the change in the P-R interval from 0.16 seconds to 0.21 seconds. Note also the absence of deflectional changes in the QRS-complex.

appear that first stage A-V block exists. A number of cases in which initial pneumothorax was instituted were studied from the electrocardiographic point of view. The changes observed are the subject of a separate communication. In the course of this study occasional prolongation of the measureable P-R interval was observed.

Figure 5A is a tracing before an initial right pneumothorax was instituted. Figure 5B is one taken immediately after 300 cc. of air was instilled into the right pleural cavity. A definite change took place in the measurable P-R interval. Two factors should be considered in the pathogenesis of this manifestation: (*1*) a sudden change in vagal tone (this will be more fully discussed later); (*2*) the effect of mediastinal shift. Since the measurable change in the P-R interval was associated with a deformed P-wave, and was found not only immediately after instillation of air but also in the tracings taken later until reëxapansion of the lung took place, the assumption that this electrocardiographic manifestation is due to anatomical intrathoracic changes, rather than to increase in vagal tone, seems probably to be the correct one. We have observed a number of cases with prolonged P-R intervals in pulmonary tuberculosis with no history or clinical findings of rheumatic fever or coronary sclerosis. They were associated with pneumothorax or other conditions causing mediastinal displacement. In most cases they were transient, disappearing when the mediastinal shift was rectified (in cases of pneumothorax by reëxpansion of the lung).

DISCUSSION

There is apparently no general agreement as yet as to the incidence of cardiac involvement in chronic pulmonary tuberculosis even when emphysema is a complicating factor (9, 10, 11). There is no doubt however that circulatory disturbances are frequently present in the clinical picture of tuberculosis, and in a number of instances constitute the primary cause of death (12, 13). The existence of *cor pulmonale* in pulmonary tuberculosis was recently reëmphasized by Scott and Garvin (14). There is a wide range in the incidence of the syndrome in the published reports, from 6 per cent to 29 per cent (15, 16, 17). The incidence in our own necropsy material is 8 per cent. It must be emphasized, however, that no case of right ventricular hypertrophy associated with left ventricular hypertrophy was included in our series. It is possible that the actual incidence of *cor pulmonale* is greater than stated, as the majority of observers stress the frequent association of left ventricular hypertrophy with *cor pulmonale* (14). However, the selection of cases with isolated right heart hypertrophy only eliminates the necessity of exclusion of arteriosclerosis and hypertension as possible complicating factors, and thus offers ample evidence that *cor pulmonale* does occur in pulmonary tuberculosis (18). This report does not deal with the pathogenesis of *cor pulmonale* in pulmonary tuberculosis, but it is noteworthy that more than half of our cases are in the younger age group without clinical evidence of emphysema.

Since the clinical, radiographic and fluoroscopic recognition of the syndrome of *cor pulmonale* offers great difficulties, the question naturally arises, how much does the electrocardiogram help? Until Winternitz in 1935 (19) drew attention to the existence of a so-called *P pulmonale*, right axis deviation was the sole electrocardiographic criterion of right heart strain. Thus, Boas and Mann (20), using this criterion, reported an incidence of 29 per cent of right heart involvement in a series of 97 patients with pulmonary tuberculosis. It was their im-

pression that displacement of the heart, which is so common in tuberculosis, and which is often extreme, ordinarily has no effect on the electrocardiogram. They observed, however, that right axis deviation is not found more frequently in association with fibroid phthisis or with pleural adhesions, than with other types of pulmonary tuberculosis, thus admitting that there is another factor outside of those known to cause circulatory embarrassment, which may cause right axis devation. Since then ample evidence has been presented of the existence of a definite effect of mediastinal shift on the electrocardiogram (3, 12). As a matter of fact, the axis of the QRS-complex can be frequently changed at will by mere change of position of the patient (*vide supra*). Right axis deviation in the electrocardiogram cannot serve therefore as a reliable criterion of the existence of *cor pulmonale*.

Winternitz (19) was the first to draw attention to the occurrence of abnormal auricular complexes in the electrocardiogram of emphysema, pulmonary tuberculosis, chronic bronchiectasis and kyphoscoliosis. These abnormalities, according to his observations, consist of a low or occasionally isoelectric P-1 and a high P-2 and P-3, spiking or having a wide summit. The base of the P-wave is not widened. Notching may occasionally occur. These observations were confirmed by Schlomka and Klein (21) and mentioned again more recently by Brill (22). However these criteria are not absolute. According to Winternitz, these P-wave changes are modified, or not present, when sclerotic changes take place in the heart; they may be present without X-ray changes of right heart enlargement; their amplitude is subject to change with respiration. He quotes Rothberger and Winterberg (23) who demonstrated that the so-called *P pulmonale* may occur as a result of exercise, and admits that in the material he studied there were occasional cases of *P pulmonale* without evidences of pulmonary hypertension. These exceptions seem to be of significance and demand a more critical approach to the evaluation of the abnormal P-wave. It is particularly important to consider the effect of mediastinal shift upon the complex. In a recent report by Ippolito and Reinstein (6), 215 tracings with characteristic P-wave alterations described, were found in a series of 6,120 electrocardiograms; "167 of them had some form of pulmonary disease capable of producing *cor pulmonale*." In this group however were 81 cases of pulmonary tuberculosis, 4 cases of bronchogenic carcinoma, 3 cases of pneumothorax and a number of other conditions capable of producing P-wave changes by virtue of mediastinal distortion. The mechanical influence of tuberculosis on the configuration of the P-wave is also suggested from such reports, as one by DeWeth (24), where in a series of 508 cases of pulmonary tuberculosis, 22 per cent presented an increase in the height of the P-wave. This high figure is analogous to the high incidence of *cor pulmonale* as based on the occurrence of right axis deviation alone (20) and like the latter probably also does not represent the actual incidence of right heart involvement in pulmonary tuberculosis, but rather represents in most cases the effect of mediastinal displacement. A more recent report by Nordenfelt (25) completely denies the existence of a pulmonary P-wave. Forty-six cases with "pulmonary P-waves," in accordance with Winternitz's

criteria, were found among 2,000 electrocardiographic tracings. Only a small number of these cases had evidence of cardiac or pulmonary involvement. The abnormal P-waves in this series are said to be due to changes in posture and in some cases to a labile autonomic nervous system. Parkinson and Hoyle (18), in reporting on the radiographic evidence of heart involvement in 80 cases of emphysema, found only 4 examples of the P modification which Winternitz had connected with this condition. Changes in the P-wave, other than those conforming to the Winternitz pattern, were found in 7 cases. It is not stated whether the cases with the P-wave changes had other pulmonary disease in addition to emphysema. It is stated, however, that pulmonary tuberculosis was an associated finding in 10 cases of the series, that 2 cases had kyphoscoliosis and that a history of haemoptysis was obtained in 20 patients, and 11 patients had a history of pleuritic pain. It is of significance that in the 11 cases which showed radiographic evidence of isolated enlargement of the right heart, "supporting electrocardiographic evidence was completely absent."

The following considerations question further the specificity of the P-wave pattern in *cor pulmonale*: (*a*) the so-called mitral P is supposed to be distinguished from the pulmonary P by the fact that the complex is notched, high and wide in leads-I and -II (19, 21). Changes in P-1 and P-2 are said to be an expression of left auricular involvement (16). However, these changes were observed only in cases where right auricular hypertrophy was shown to be present in addition to hypertrophy of the left auricle (27). Thus, right auricular involvement does not influence the P-wave changes in leads-II and -III exclusively. Conversely, left auricular dilatation will not necessarily affect the P-waves in leads-I and -II only. Master (26), studying the P-wave in tracings of acute coronary occlusions, found definite changes in 32 out of 40 cases. Twenty times the P-wave was most prominent in leads-I and -II and on 11 occasions in leads-II and -III. He suggests that P-wave changes in leads-I and -II are associated with left auricular dilatation, a sequence to infarction in the left ventricle. We doubt the correctness of this conclusion as the occurrence of P-2 and P-3 changes in 11 out of 32 cases is a ratio too high to be explained on a basis of the incidence of right ventricular infarction. (*b*) Figure 6A represents a tracing taken on a patient at the time when an X-ray film of his chest revealed a large pneumothorax with displacement of the mediastinum to the left (figure 7). Ten months later a massive empyema developed on the side of the pneumothorax with further displacement of the mediastinum to the left. An electrocardiographic tracing corresponding to that period is seen in figure 6B. The marked change in the amplitude of P-2 and P-3 is obvious. The prominent P-2 and P-3 in figure 6A can therefore not retain their significance as evidence of *cor pulmonale*. Apparently, anatomical displacement, or possibly such physiological factors as changes in intrathoracic pressure, determines the configuration of the auricular complex in this case.

Such changes in the P-wave may, as stated above, at times alter the measurable P-R interval and lead to the suspicion of a shift in the pacemaker. Figure 8A is a tracing taken of a patient with chronic pulmonary tuberculosis, pul-

monary fibrosis and emphysema. It presents right axis deviation and an accentuated and notched P-2 and P-3. Fluoroscopic examination of the patient revealed the mediastinum, particularly the vascular area, to be displaced to the left; the heart was not enlarged. Nine days prior to the date of tracing 8B, the patient began to show ankle oedema. Right heart failure was progressively increasing and digitalis was administered. He received 18 cat units of the drug

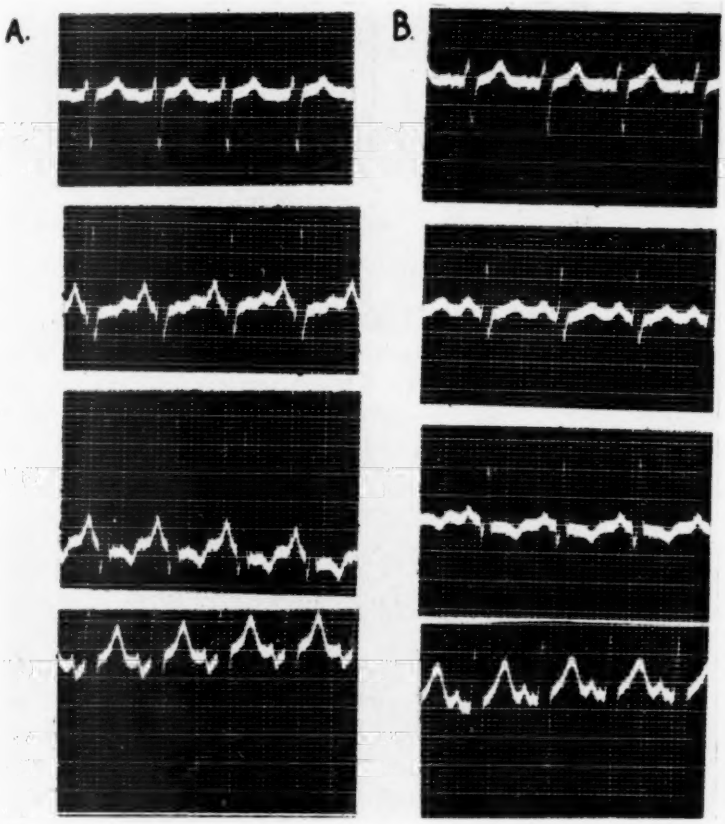

FIG. 6. *The effect of changes in intrapleural pressure on the electrocardiogram.* A. Electrocardiographic tracing of a case with a large right pneumothorax. Note the RAD, inversion of P-1 and tall P-2 and P-3.

B. Electrocardiographic tracing of the same patient ten months later, when a massive pyopneumothorax developed in his right chest with further displacement of the mediastinum to the left. Note the change in the amplitude of P-2 and P-3 to normal.

in the four days preceding the date of tracing 8B. The shortening of the P-R interval (lead-II) from 0.16 seconds (figure 8A) to 0.12 seconds (figure 8B) and the diphasic P-wave suggest a shift in the pacemaker. That this is not the case and that the phenomenon is due to the displacement of the mediastinum, is seen from the fact that changes in the QRS-complex took place simultaneously. The R-1 in figure 8A is larger than the R-1 in figure 8B; QRS-2 in figure 8B is

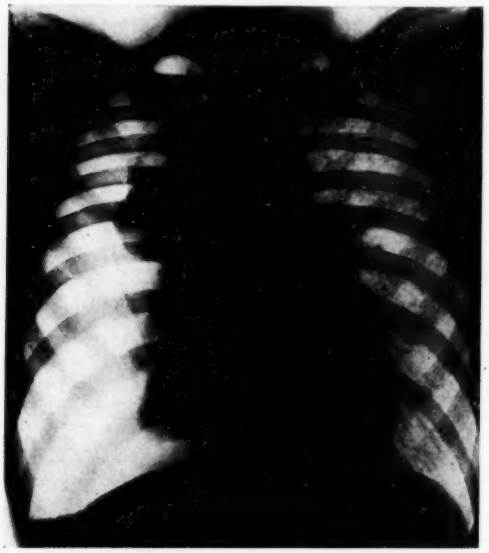

FIG. 7. *X-ray film of chest of patient whose electrocardiographic tracings are recorded in figure 6.* Chronologically, this plate corresponds to tracing in figure 6A.

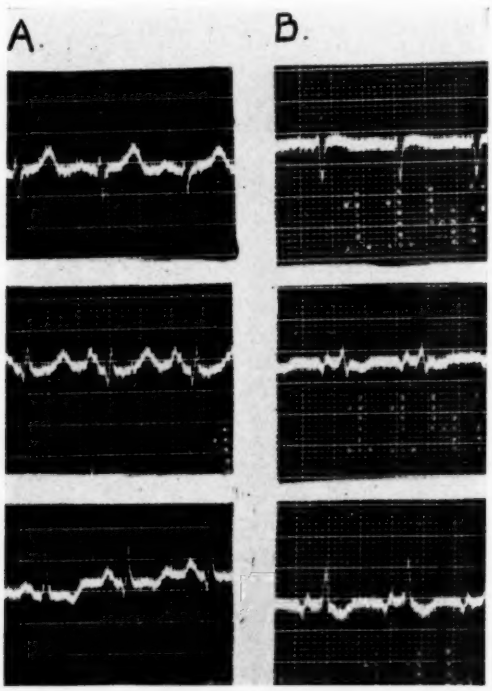

FIG. 8. *Changes in the P-wave simulating those due to shift of the pacemaker.* A. Electrocardiographic tracing of a patient with bilateral pulmonary tuberculosis and emphysema.

B. Tracing taken nine days later. See text for explanatory notes.

the mirror image of the QRS-2 in figure 8A; and there is a Q-3 in figure 8A which is absent in figure 8B. Such changes are not produced by digitalis. This case again illustrates the instability of the P-wave in cases with gross pulmonary disease, and thus undermines the validity of this complex as a criterion of *cor pulmonale.*

Analysis of our clinical material almost tempts us to admit the association of a low P-1 and an abnormal P-2 and P-3 with emphysema, as this association took place in about 50 per cent of our cases. However, our necropsy material does not supply confirmatory evidence. The above illustrations and the experimental section of our report seem to denude the abnormal P-wave entirely of its "special" significance.

How the positional change influences the configuration of the P-wave can, at this stage, be answered only hypothetically. *It probably involves the change in the relationship between the auricular tissue and the conductors.* In commenting on the P-wave changes in acute coronary occlusion, Master (26) states, "The increase in size of the P-wave may be due to change in position of the auricles or perhaps due to a transient enlargement of these chambers." The latter hypothesis is held by the author to be probably the correct one because no directional changes of the QRS-complex occurred in his series. This argument, however, is not convincing, as seen in the results of our experiment with positional electrocardiograms, where the P-waves always altered their shape with change in position, while the QRS-complex did so only in 60 per cent of the cases. On the other hand, transient distension of the right auricle, at least as attempted by us, apparently does not alter the form of the auricular complex. It is conceivable that in acute coronary closure with infarction, particularly when large, a change takes place in the mass relationship of the ventricles, disturbing the relative position of the auricles, and thus influencing the shape of the P-wave. In the case of auricular hypertrophy, the altered relationship between the auricular muscle and its anatomical environment may explain the altered P-wave. The same explanations can be offered, with some hesitancy however, for the occurrence of two P-waves separated by an interval of 0.1 seconds in the case of an aneurism of the left auricle reported by Mahaim (28).

It is of interest to note that right pneumothorax was almost invariably associated with an inversion of P-1. It is not improbable that in this condition a *certain* anatomical arrangement is created involving the right (and possibly also the left) auricle in relation to the environment. This could be achieved either by a simple mechanical distortion, as P-1 inversion is also occasionally seen in cases of left lung retraction or by changed intrathoracic dynamics reflecting itself in the intravascular (venae cavae) or intra-auricular tension.

Another hypothesis, involving neurogenic influences, cannot be dismissed completely. Einthoven (29), while studying the effect of vagal stimulation on the electrocardiogram of a dog under chloroform anaesthesia, which is in itself known to increase vagal tone, found that, while no change occurred in the QRS-complex, the auricular complex changed from normal to diphasic. Ritchie (30) demonstrated lengthening of the auricular systole in one human heart during

compression of the right vagus. This observation of Ritchie may possibly supply an explanation for the electrocardiographic picture in figure 5. Other functional derangements of the heart, such as premature contractions, were observed by Natin (31) in cases of pneumothorax and by Fortunato (32) in cases of pneumothorax with mediastinal hernia. These functional derangements may be explained by the disturbed relationship and tension of the cardiac nerves which probably take place with the torsion and angulation of the great vessels (13).

There are only two experiments available in the literature bearing on the pathogenesis of the abnormal (notched) P-wave. In the one of Lewis (33) notching and increase in amplitude of the P-wave were caused by crushing one auricular appendage. Rothberger and Scherf (34) produced notching, flattening and inversion of the P-wave by ligations of the interauricular bundle. Bachman (35) reported histological evidences of degenerative changes in the interauricular band in a case showing splitting of the P-wave. It is his opinion that direct injury to the interauricular bundle or serious interference with its blood supply will delay interauricular conduction, and that this will manifest itself in the electrocardiogram as a split P-wave.

It is doubtful, however, whether such organic changes can explain the P-wave abnormalities presented in this communication.

SUMMARY AND CONCLUSION

Electrocardiographic tracings of 804 patients with pulmonary tuberculosis were analyzed with particular reference to the occurrence of abnormal auricular complexes.

Sixty-nine tracings were found to possess abnormal P-waves; 38 tracings in this group had notching and spiking in leads-II and -III; 16 out of the 38 tracings were associated with clinical and roentgenological evidence of bilateral tuberculosis and emphysema.

Fifteen cases of severe emphysema were studied electrocardiographically. 8 cases had a low P-1 and a notched and spiked P-2 and P-3.

Fifteen cases with postmortem evidence of right ventricular hypertrophy without hypertrophy of the left ventricle showed findings not fully confirmatory of the observations stated above. The predominant electrocardiographic abnormality in this group was an abnormal P-2.

To study the effect of change in position on the auricular complex, 10 cases with changes in the P-wave of lead-I had electrocardiograms taken in the supine, left lateral and right lateral positions. Only 6 cases had directional changes in the QRS-complex. All cases showed changes in the configuration of the P-wave with change of position of the patient.

In order to see the effect of transient overfilling of the right auricle on the electrocardiogram, 10 patients in congestive failure with enlarged livers and prominent jugular veins, had tracings taken prior to, and after, pressure upon the liver sufficient to increase the volume of the jugular veins to a marked extent. No change in shape or amplitude of the previously normal P-waves in the 8 cases with sinus rhythm took place.

It is our impression that P-wave changes cannot serve as a criterion for the existence of *cor pulmonale* in cases of pulmonary tuberculosis (or other gross pulmonary disease) where such information is most desirable. On the other hand, P-wave changes are frequently the sole electrocardiographic evidence of mediastinal displacement.

In the course of this study two additional interesting observations were made:

(*1*) In a limited number of cases studied, inversion of the P-1 was almost universally associated with displacement due to right pneumothorax.

(*2*) Changes in the measurable P-R interval in the electrocardiogram of cases with pulmonary tuberculosis may be due to mediastinal displacement or distortion. These changes are probably expressions of structural divergences of the P-waves and not indicative of altered A-V conduction or shift in the pacemaker.

SUMARIO Y CONCLUSIONES

Analizáronse los trazados electrocardiográficos de 804 tuberculosos pulmonares, con referencia particular a la aparición de complejos auriculares anormales.

Sesenta y nueve trazados revelaron ondas-P anormales, mostrando 38 de ellos escotaduras y espigas en las derivaciones II y III, asociándose 16 de los 38 con signos clínicos y roentgenológicos de tuberculosis y enfisema bilaterales.

De 15 casos de enfisema grave estudiados electrocardiográficamente, 8 revelaron depresión de la onda P-1, y escotaduras y espigas de las ondas P-2 y P-3.

En 15 casos con signos autópsicos de hipertrofia ventricular derecha sin hipertrofia del ventrículo izquierdo, los hallazgos no confirmaron por completo dichas observaciones. La anomalía electrocardiográfica predominante en este grupo correspondió a la onda P-2.

A fin de estudiar el efecto del cambio de posición sobre el complejo auricular, en 10 casos con alteraciones en la onda-P de la derivación I, obtuviéronse electrocardiogramas en las posiciones supina, lateral izquierda y lateral derecha, y sólo 6 revelaron cambios de dirección en el complejo QRS. En todos los casos cambió la configuración de la onda-P al variar la posición del enfermo.

Tratando de observar el efecto sobre el electrocardiograma de la repleción parcial del aurículo derecho, obtuviéronse trazados de 10 enfermos con insuficiencia congestiva, hepatomegalia y venas yugulares prominentes, tanto antes como después de comprimir el hígado lo suficiente para hacer aumentar marcadamente el volumen de las venas yugulares. No se observó alteración alguna en la forma o amplitud de las ondas-P previamente normales en los 8 casos con ritmo sinusal.

Las alteraciones de la onda-P no pueden, pues, servir de pauta para la existencia de *cor pulmonale* en casos de tuberculosis pulmonar (u otra afección pulmonar macroscópica), en que dicha información resultaría utilísima. En cambio, las alteraciones de la onda-P constituyen con frecuencia la única prueba electrocardiográfica de desplazamiento del mediastino.

Al realizar este estudio, hiciéronse otras dos observaciones interesantes:

(1) En un número limitado de casos estudiados, la inversión de la onda P-1 se asoció casi siempre con desplazamiento debido a neumotórax del lado derecho.

(2) Las alteraciones en el intervalo P-R mensurable del electrocardiograma de casos de tuberculosis pulmonar, quizás se deban a desplazamiento o distorsión del mediastino, constituyendo probablemente la expresión de divergencias estructurales de las ondas-P, sin ser indicativas de cambios de la conducción A-V o desviación del nódulo sinoauricular.

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PULMONARY MANIFESTATIONS IN EXTRAPULMONARY TUBERCULOSIS[1]

A Roentgenological Study of 100 Cases

LEO TEPPER AND GEORGE JACOBSON

Long before the aetiology of tuberculosis was proven, it was realized by many that caries of the spine, swollen and painful joints, and enlarged lymph nodes often coexisted with pulmonary disease. In the early part of the nineteenth century, Pierre Louis made the statement, later to be known as Louis' law, that "tuberculosis of any part is attended by tuberculosis of the lungs."

In recent years numerous studies have been made to determine the status of the lungs in patients with extrapulmonary tuberculous lesions. The problem has been approached from two directions: first, by those mainly concerned with surgical tuberculosis who have attempted to note the frequency with which pulmonary tuberculosis was present in their patients and what effect its presence had upon the course of the extrapulmonary disease and, second, by pathologists and clinicians who have attempted to study and analyze the form and character of the pulmonary lesions accompanying surgical tuberculosis.

A review of the literature reveals these observations:

First: A large proportion of cases with extrapulmonary tuberculosis have associated intrathoracic lesions.
Second: These pulmonary lesions are apparently of haematogenous origin.
Third (and probably the most interesting observation): These pulmonary lesions of haematogenous origin often result in a chronic form of pulmonary tuberculosis which definitely differs from the usual adult reinfection type.

Though statistics vary, the consensus is that a large percentage of patients with extrapulmonary tuberculosis have coexisting pulmonary disease. McKinnon (1) in 1924 showed that two-thirds of his patients over sixteen years of age with bone and joint tuberculosis had pulmonary involvement. Snyder (2) demonstrated 40 per cent of his cases with pulmonary lesions, Meng and Chen (3) 47 per cent and Ragolsky (4) in a study of 200 cases with roentgenograms of the chest demonstrated that 55 per cent of his cases had intrathoracic lesions. In 1933 the American Orthopaedic Association Committee reported that 37 per cent of patients with fatal osseous or joint tuberculosis showed active pulmonary tuberculosis. Rosenkrantz, Piscitelli and Bost (5) reported a series of 160 cases with 74 per cent having evidences of pulmonary involvement—60 of them with far advanced disease. These latter workers state that "Though constantly requiring reëmphasis, it is well known that tuberculosis of bone and joint is usually secondary to some primary tuberculous focus. The treatment of bone and joint disease cannot be considered independently of treatment of the general infection." McKenna and Sweany (6) stress the haematogenous nature of kidney tuberculosis, and the association with pul-

[1] From the Los Angeles County Hospital, Los Angeles, California.

monary disease is reported by Jameson (7) and Greenberger, Wershub and Auerbach (8). The relationship between extrapulmonary and pulmonary tuberculosis is also discussed by Renaud (9), Alexander (10), Petter (11), and Marienfeld (12).

Emphasis is placed upon the systemic nature of tuberculosis, upon the fact that the lesions in bone, joint or kidney are secondary to some primary focus from which the blood stream has carried the organisms to their terminal sites; that no matter what the portal of entry, bacilli carried by the blood must frequently come in contact with the lung prior to the invasion of the systemic circulation; and that in a certain proportion of these cases the lung in its filtering capacity will also show varying degrees of involvement. It is also pointed out that from the usual focus within the lung the bacilli may be carried by way of the lymphatics to the venous return and the right heart, once more to be returned to the pulmonary capillary bed, and that the degree of filtering and dosage of bacilli will determine whether the seeding is limited to the lesser circuit or spread by way of the systemic circulation. Furthermore, it is possible that the extrapulmonary foci themselves disseminate bacilli at varying intervals, thus producing pulmonary lesions secondarily by way of the blood stream.

THE CHARACTER OF THE LUNG LESIONS

Following Ranke's (13) classification of tuberculosis as a systemic disease in 1916, the literature, especially the foreign literature (14, 15, 16, 17), has contained numerous references to a haematogenous form of chronic pulmonary tuberculosis, the characteristics of the lung lesions being discussed at length by Miller in this country and by Pagel and many other pathologists and clinicians abroad.

Miller (18) in discussing haematogenous pulmonary tuberculosis makes the statement that, "inasmuch as the haematogenous origin of the proved extrapulmonary tuberculosis is indisputable, a similar explanation for the intrapulmonary lesions appears equally certain." Pagel (19) in a masterly analysis of autopsies of 83 cases of extrapulmonary tuberculosis has stressed the haematogenous nature of the associated pulmonary lesions and described their essential characteristics. Reissner (20) in a study of the relations between extrapulmonary and pulmonary tuberculosis concludes that, "The pronounced morphological and topographical similarities between the chronic disseminated forms and the acute miliary disseminations and particularly the frequent occurrence of the former in association with extrapulmonary tuberculosis are decisive points in favor of their haematogenous origin." Incidentally Reissner found that more than one-half of his cases demonstrated postprimary pulmonary involvement. Pinner (21), in discussing a series of haematogenous pulmonary tuberculosis cases, gives the criteria for the assumption of haematogenous genesis of a pulmonary lesion as: the frequent association of extrapulmonary lesions, the tendency to evenly distributed lesions, and the frequent absence of older pulmonary foci from which bronchogenic spread could have occurred.

The essential features, found singly or in combination, of this form of tuberculosis as compiled from the literature are:

1: Inconspicuous bronchogenic spread.
2: A picture like miliary tuberculosis but with sharply defined fibrotic nodules, fewer in number than in acute dissemination.
3: A focus in one apex—often calcified—similar to Simon's focus.
4: A diffuse emphysema produced by fibrotic contracture of numerous small nodules.
5: Predominance of fibrosis and calcification.
6: Solitary, encapsulating, calcifying foci in the upper parts of the lung.
7: Thin-walled, punched-out cavities.
8: Involvement of pleura often without parenchymal lesions.

Pagel states that these features are not only characteristic and that they definitely differentiate this form of postprimary pulmonary tuberculosis from the more common form of isolated organ pulmonary tuberculosis, but also that these two forms are mutually exclusive—that the presence of one excludes the other. He attempts to explain the tendency toward chronicity and stability in the majority of cases of chronic haematogenous pulmonary tuberculosis upon an immunological tissue response produced by the dissemination of the bacilli.

The purpose of this paper is to present the results of an analysis of the roentgenological picture of the chest in 100 cases of extrapulmonary tuberculosis; and to compare these results with the roentgenological findings in 100 adult pulmonary tuberculosis cases without evident extrapulmonary disease, in an attempt to substantiate the above observations and to determine whether a characteristic roentgen picture can be formulated and recognized as of haematogenous origin, and whether or not such knowledge can be of practical import to the clinician in his management of tuberculosis.

NATURE OF MATERIAL

One hundred consecutive cases of extrapulmonary tuberculosis with one or more chest films were selected from the files of the Los Angeles County Hospital for analysis. These cases were seen on the wards or the clinics from 1930 to 1941. Patients under fifteen years of age were not considered and tuberculous laryngitis and enteritis were excluded from the extrapulmonary group because of their contact character in the majority of instances. Tuberculosis of the skin and eye were also excluded as was acute tuberculous meningitis and all other extrapulmonary foci of recent nature, presumably resulting from a terminal dissemination of a far advanced pulmonary tuberculosis.

The types of extrapulmonary lesions studied in this series included:

Skeletal	37
Genito-urinary	29
Adenitis	13
Peritonitis	3
Tuberculoma of brain	1
Combined lesions	17

Approximately 50 per cent of the cases demonstrated skeletal involvement either alone or in combination with some other focus. In many of the skeletal lesions positive biopsy reports were obtained but when not available roent-

genological diagnosis of their tuberculous aetiology was accepted. All other lesions were accepted only when there was actual pathological or bacteriological proof of tuberculosis.

The majority of patients, 68, were between fifteen and forty years of age. Only 32 cases were over forty, with 20 of these between the ages of fifty and seventy-four. There were 65 males and 35 females in the group. This distribution was not remarkable since it paralleled that of the admissions to the tuberculosis service.

ANALYSIS OF RESULTS

Out of the 100 cases, 79 had postprimary tuberculous involvement of varying degree. Twenty-one revealed normal chest films as far as postprimary tuberculosis was concerned; 8 of this group showed evidence of primary infection, however, either a Ghon focus or glandular calcifications or both. Thirty-four of the total 100 showed evidence of primary infection in the past.

Types of postprimary parenchymal lesions: In the 79 cases evidencing postprimary tuberculosis, the outstanding feature was the tendency to calcification and fibrosis; 37 of the cases showed fibrotic changes on the film—24 of this group being predominantly fibrotic. Calcification appeared upon 35 of the films—12 of these cases having predominantly calcified lesions. Sweany (22), in his paper discussing pulmonary calcifications, points out that any parenchymal tuberculous lesion may calcify with time and Pinner (21) states that he has "seen cases in which calcification developed from lesions which were obviously not haematogenous." Nevertheless, calcification certainly is not a prominent or frequent finding in ordinary adult postprimary tuberculosis and furthermore the large majority of calcifications in this series were symmetrically distributed which would seem to point to haematogenous origin.

Exudative manifestations were noted in 18 cases but in only 2 of these did the exudative phenomena predominate.

Proliferative lesions were present in 36 of the cases; in 3 proliferation was the predominant roentgen feature. Proliferation as used in this paper is defined as a lesion between the exudative and fibrotic, apparently of a more granulomatous character with tendency to become linear but with no evidence of the contraction noted in fibrosis.

Nodular lesions were present in 25 cases; in 5 this was the predominant feature.

Twelve cases showed a miliary type of picture, 7 of these acute. Five were of a chronic nature corroborated by their course, with fibrocalcific lesions more discrete and fewer in number than in the acute form.

Gross emphysema was noted in 5 cases.

Location: Sixty-eight of the 79 showed supraclavicular involvement, 14 predominantly so. Fifty-seven also had subapical involvement, 7 of this group being predominantly subapical. Thirty-one had midlung involvement but in only one was this the predominant site. Eleven cases, all in the miliary group, had basal involvement. Thus the preponderance of lesions was of apical and

subapical distribution and the bases were spared except in those cases which appeared to be of diffuse haematogenous nature.

Symmetry: Twenty-two of the group demonstrated only unilateral lesions; 13 were bilateral with one side predominantly involved, while 44 cases, or about 55 per cent of those having postprimary pulmonary lesions, had bilateral lesions which were symmetrical.

Course: Many of the cases had only one chest film taken at the time of the diagnosis of extrapulmonary tuberculosis or as an aid to that diagnosis. Often when the film of the chest revealed an apparently inactive parenchymal involvement no further films were taken. Of 41 cases having only one chest film, 23 had what was interpreted as a chronic appearance—that is, mainly fibrotic or fibrocalcific lesions. Five of this group showed a diffuse nodular seeding giving a miliary appearance but were of discrete and fibrotic character and had a known chronic course. Only 3 of the 41 had a preponderantly exudative caseous appearance. Seven cases had a picture typical of acute miliary tuberculosis. In 8 cases no definite interpretation of activity could be made.

The remaining 38 cases with postprimary involvement had more than one chest film taken with the intervening time varying from three months to eight years. In these cases an attempt was made to estimate progression, regression or stability of the lesion. Of these 38 cases, 4 showed evidence of progression—at least one of these demonstrating a haematogenous form of progression rather than bronchogenic. Eleven of this group showed regression and 23 evidenced stability or no essential change in the time folllwed.

Cavity: Fifteen of the 79 cases showed cavitation. Twelve of these had a positive sputum (1 was negative and in 2 there was no record), whereas the majority of cases without excavation had negative sputa. This group with cavity also evidenced symptoms referrable to the chest, such as cough, sputum and occasional haemoptysis. Of the cases with more than one chest film in this group only one demonstrated definite bronchogenic progression; 2 evidenced regression and 5 cases showed no apparent change, one of these over a two-year period. One case with cavity showed regression of the excavation but at the same time an associated apparently haematogenous spread. Of the remaining cases, 2 appeared to be of the chronic fibrotic contractive type while 2 appeared to be part of a rather soft active recent process. The 2 remaining cavity cases could not be grouped as to activity.

Ten of these cases had cavities with apparent thin walls. Three had definitely thick walls and 2 were questionable. Two of the cavities were apparently superimposed upon an old apical and subapical fibrocalcific lesion of the type so often seen in the other films.

In 9 of the cases the cavities were bilateral and fairly symmetrically arranged.

Pleural involvement: There were 10 cases with pleural effusion, 3 of them having bilateral involvement. Only one of this group had no parenchymal lesion. Apical caps were demonstrated in 24 of the 79 cases; 12 of these were bilateral. Jamison (23) points out that many of these apical scars may well be nontuber-

culous in origin. Lateral thickening was seen 26 times, 3 times bilaterally and one of this group demonstrated calcification of the pleura.

Symptomatology and sputum: Only 6 cases of the group without cavity were recorded as having positive sputa. Similarly in most cases localizing pulmonary symptoms were inconspicuous. In fact, pulmonary lesions often seemed to be just an accidental discovery. With the preponderance of apparently inactive fibrocalcific lesions this is not surprising. When breakdown was present symptoms of cough and sputum usually were present; but in some of these, symptoms and physical findings were not as pronounced as one might have deemed likely.

Comment

A review of our findings in this study would indicate that pulmonary postprimary lesions are frequently found in association with an extrapulmonary tuberculous focus; that these lesions within the lung differ in appearance from the usual postprimary adult type tuberculosis. They usually show marked evidence of healing, are in the main fibrous or calcific and apparently are the remains of an ancient infection; they are presumably inactive and bear very little clinical significance other than that their presence emphasizes the systemic character of the disease process. The age of these lesions, their tendency toward bilateral symmetrical distribution, their frequent association with evidences of primary pulmonary lesions and their frequent appearance in patients having extrapulmonary tuberculosis make their haematogenous origin a logical assumption.

Whether more recent pulmonary infection or superimposed infection in this type of case will still tend toward chronicity is difficult to prove. It is conceivable that a completely healed haematogenous spread may no longer have any effect upon future disease. The infrequency, however, of the usual picture of isolated organ pulmonary tuberculosis with its tendency to bronchogenic transmission in this series might be taken as an indication of some degree of increased local resistance in these cases.

It has been pointed out by Reissner, Cohen (24) and others that the usual form of chronic pulmonary tuberculosis may be superimposed upon former haematogenous foci and may progress so as to be indistinguishable from the usual adult reinfection pulmonary tuberculosis. Pinner (21) describes the haematogenous foci as being mainly interstitial, but points out that they may break through to alveolar and intracanalicular spread. However, although in a small series, those of our cases with excavation and positive sputum on the whole showed a decided disinclination toward bronchogenic spread and thin-walled cavities had little of the soft caseation so often noted in the usual adult reinfection tuberculosis.

ANALYSIS OF ONE HUNDRED CASES OF ISOLATED PULMONARY TUBERCULOSIS

As a control, a review of the chest films of the first 100 patients admitted to the Los Angeles County Hospital Tuberculosis Unit after January 1, 1941 was made. These patients exhibited no clinical evidence, past or present, of extrapulmonary tuberculosis.

Of the significant contrasting findings in this group, the most conspicuous feature was the exudative caseous nature of the lesions with tendency toward bronchogenic spread. Eighty-three of the cases showed lesions interpreted as exudative and, in 70 of these, exudation was the predominant lesion.

Fibrosis was present in 33 cases, but in only 6 was it the predominating lesion; while calcification, so frequently noted in the extrapulmonary group, was found in only 3 patients and in none of these was it a predominant feature.

Two patients in this group showed the picture of acute miliary tuberculosis against 7 of the 79 in the extrapulmonary group. These numbers are too small for any conclusion to be drawn, but it has been noted in the literature that there is a much greater tendency for individuals with extrapulmonary tuberculosis to die of an acute haematogenous spread rather than of bronchogenic progression of a pulmonary lesion.

Evidences of primary pulmonary lesions were rare, parenchymal calcifications being seen on 3 occasions and glandular calcifications also being noted 3 times. This was in rather marked contrast to the findings in the extrapulmonary group.

Location: The great majority of the cases were far advanced and all portions of the lung were involved, the apical and subapical areas most frequently. Of note, for comparison, was the coincident basal involvement seen in 40 cases. This, in association with the asymmetrical character of the lesions so often noted, would seem to be further evidence for the tendency to bronchogenic progression in this group. Bilateral involvement with one side predominating was noted in 70 of the 100 cases.

Course: Of 62 patients with more than one chest film, 19 showed evidence of bronchogenic progression. Of 38 patients with but one chest film, 35 were interpreted as of acute nature. Many of these were terminal upon entry and expired before a second film was taken. Only one of this group was adjudged to be of chronic nature. This is in marked contrast to the 4 per cent interpreted as of acute appearance in the extrapulmonary group and the 29 per cent of chronic nature.

Cavity: Of the 64 cases with cavity, 41 were thick-walled with surrounding parenchymal involvement. These were usually asymmetrical in distribution and tended toward bronchogenic spread much more frequently than those of the extrapulmonary group.

Just as interesting was the discovery in the study of this group that approximately 10 per cent had pulmonary lesions characteristically seen in the lungs of the extrapulmonary group. A few of these with bilateral, symmetrical apical and subapical fibrosis and nodulation with a tendency toward chronicity, and a few with symmetrical thin-walled cavities with a tendency to contraction and healing, seemed to fit the picture of chronic disseminated pulmonary tuberculosis very well. Whether an unrecognized extrapulmonary focus was present in these cases is open to speculation.

Comment

It must be understood that the overwhelming preponderance of acute exudative caseous lesions with tendency to bronchogenic spread in the comparison

group was to be expected because of the many acutely ill, often terminal patients admitted to the Los Angeles County Hospital Tuberculosis Unit. Because of this, the contrast between the lesions in this group and those in the extrapulmonary group is probably overemphasized. Nevertheless, there does seem to be a valid difference between these two forms of pulmonary tuberculosis, recognizable on the roentgenogram.

Without treading upon the controversial ground of the endogenous origin of the usual adult pulmonary tuberculosis, it can be predicated that some forms of chronic pulmonary tuberculosis appear to be of haematogenous origin. This chronic haematogenous pulmonary tuberculosis is most often associated with extrapulmonary tuberculosis but the characteristic pulmonary lesions may be found when there is no clinically evident extrapulmonary focus.

It is important to recognize this form of disease because of the apparent tendency to relatively benign and chronic course. Pagel believes that the dissemination of bacilli produces some form of immunological tissue change resulting in heightened resistance to local infection. In this connection, it is interesting to note that Pinner (25) in discussing noncaseating tuberculosis stresses the widely disseminated character of this type of disease.

In the light of our present knowledge, presumably all degrees of haematogenous spread occur following a primary implantation and the immunological response must be of great variability and complexity. In addition, all degrees and forms of pulmonary involvement will also present themselves, including borderline cases not possible to classify as of haematogenous origin with the characteristics attributed to this type. But if and when it is possible to recognize a lesion or form of disease which seems to exhibit evidences of heightened resistance, it should be valuable from both prognostic and therapeutic standpoints.

The haematogenous form of pulmonary tuberculosis should be recognized by the surgeon treating extrapulmonary tuberculosis so that he may evaluate the disease properly. The relative frequency with which pulmonary tuberculosis complicates an existing extrapulmonary focus should be kept in mind as well as the systemic character of the disease and the need of treating the patient as a whole. Furthermore, indicated surgical procedures for the extrapulmonary focus should not necessarily be avoided because of extensive pulmonary involvement until the tendency towards stable course in this form of pulmonary tuberculosis is taken into careful consideration.

The chronic form of pulmonary tuberculosis which fits the picture of chronic dissemination should be recognized by the internist and such recognition should bring to mind the possibility of extrapulmonary foci. Furthermore, when such pulmonary lesions are suspected, prognosis and treatment should be weighed carefully in view of the apparent tendency to resistant response in many individuals having such tuberculosis. It would seem that the approach to the problem should be conservative with a not too hurried initiation of collapse procedures which otherwise might be thought indicated. It could be very possible that some of the remarkable cures with pneumothorax, phrenic or other collapse procedures were obtained not because of the collapse measures

instituted, but because of the type of disease treated. If this were true, perhaps some of the failures of treatment, because of complications of collapse therapy, could have been avoided.

SUMMARY AND CONCLUSIONS

1. The chest films of 100 unselected patients with extrapulmonary tuberculosis were analyzed in an attempt to determine the relative frequency and character of coexisting pulmonary tuberculosis. For the sake of comparison and in order to weigh the practical import of results more carefully, another 100 cases of adult pulmonary tuberculosis with no clinical evidence of extrapulmonary tuberculosis were reviewed.

2. In the group of 100 patients with extrapulmonary tuberculosis, 79 showed roentgenological evidence of postprimary pulmonary involvement. The pulmonary lesions in the majority of these 79 cases were fibrotic and calcific, apparently inactive, with proliferative, nodular and exudative manifestations decreasingly common in this order.

3. The character of these lesions, their tendency toward bilateral, symmetrical apical and subapical distribution, seen in 44 of the 79 cases, would seem to indicate a haematogenous origin and emphasize the systemic nature of the disease.

4. Roentgenographic evidence of cavitation was seen in 15 cases. These cavities were mostly thin-walled with bilateral symmetrical distribution and, in spite of the fact that 12 of these cases had positive sputa, only one showed evidence of bronchogenic spread.

5. In cases in which multiple films were available, stability or regression of the pulmonary lesion and the absence of bronchogenic spread were the outstanding features. Though progressive pulmonary lesions did occur, for the most part they were of haematogenous nature.

6. The following features, as determined from this study, may be listed as characterizing the pulmonary lesions associated with extrapulmonary tuberculosis:

(*a*) Predominance of fibrocalcific lesions, apparently inactive.
(*b*) Bilateral, symmetrical apical and subapical distribution.
(*c*) Cavities, when present, thin-walled and with tendency to symmetrical distribution.
(*d*) Relative absence of bronchogenic dissemination.
(*e*) Evidence of regression or stability in the pulmonary lesion with superimposed haematogenous spread a not uncommon feature.

7. Review of the chest films of 100 control patients admitted to the tuberculosis unit with no clinical evidence of extrapulmonary tuberculosis emphasized the acute exudative caseous nature of the usual adult pulmonary tuberculosis with its tendency to bronchogenic spread.

8. However, a small percentage of the patients in the control group without evidence of extrapulmonary tuberculosis exhibited a pulmonary picture similar to that found in the group with known extrapulmonary foci. These few cases

demonstrated bilateral, symmetrical lesions with tendency to chronic course and absence of bronchogenic spread.

9. The ability to recognize the chronic disseminated or haematogenous form of pulmonary tuberculosis would seem to be of value in prognosis and treatment to both the surgeon interested in treating extrapulmonary tuberculosis and the tuberculosis specialist.

SUMARIO Y CONCLUSIONES

1. Tratando de determinar la relativa frecuencia y naturaleza de la tuberculosis pulmonar coexistente, analizáronse las películas torácicas de 100 enfermos de tuberculosis extrapulmonar, tomadas al azar. Para fines de comparación y a fin de determinar más cuidadosamente el valor práctico de los resultados, estudiáronse otros 100 casos de tuberculosis pulmonar del adulto, pero sin signos clínicos de tuberculosis extrapulmonar.

2. En el grupo de los 100 primeros casos, 79 revelaron signos roentgenológicos de invasión pulmonar post-primaria, siendo las lesiones pulmonares en la mayoría de ellos fibrosas y calcificadas y al parecer inactivas, mientras que las manifestaciones proliferantes, nodulares y exudativas descendían en el orden en que se enumeran.

3. La naturaleza de estas lesiones y su tendencia a una distribución bilateral, simétrica, apical y subapical, según se observó en 44 de los 79 casos, parecen indicar origen hemático y recalcan la naturaleza orgánica de la dolencia.

4. En 15 casos observáronse signos roentgenográficos de cavernas, en su mayoría de paredes delgadas, con distribución simétricamente bilateral, y aunque en 12 el esputo era positivo, sólo uno reveló signos de propagación broncógena.

5. En los casos en que se contaban con películas múltiples, las características sobresalientes consistieron en estabilidad o regresión de la lesión pulmonar y ausencia de propagación broncógena. Aunque había lesiones pulmonares evolutivas, en su mayor parte eran de naturaleza hematógena.

6. Las siguientes características observadas en este estudio, pueden considerarse como propias de las lesiones pulmonares asociadas con tuberculosis extrapulmonar:

(*a*) Predominio de lesiones fibrocalcificadas, aparentemente inactivas.
(*b*) Distribución bilateral, simétrica, apical y subapical.
(*c*) Cavernas, cuando las hay, de paredes delgadas y con tendencia a una distribución simétrica.
(*d*) Relativa ausencia de diseminación broncógena.
(*e*) Signos de regresión o estabilidad de la lesión pulmonar, sin que sea rara la propagación hematógena sobrepuesta.

7. El estudio de las películas torácicas de 1000 testigos recibidos en la unidad tuberculosa sin signos clínicos de tuberculosis extrapulmonar pone de relieve la naturaleza exudativa-caseosa aguda de la tuberculosis pulmonar del adulto y su tendencia a la propagación broncógena.

8. Sin embargo, un pequeño porcentaje de los enfermos del grupo de testigos sin signos de tuberculosis extrapulmonar, manifestaron un cuadro pulmonar semejante al observado en el grupo en que había focos extrapulmonares conocidos. Esos pocos casos revelaron lesiones simétricas bilaterales, con tendencia a la cronicidad y falta de propagación broncógena.

9. La capacidad para reconocer la forma difusa o hematógena crónica de la tuberculosis pulmonar parece resultar útil en el pronóstico y tratamiento, tanto para el cirujano interesado en tratar la tuberculosis extrapulmonar, como para el tisiólogo.

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ERYTHEMA OF THE EXTREMITIES IN TUBERCULOSIS[1]

LEWIS S. TROSTLER[2]

Clinical observers in contact with patients having pulmonary tuberculosis must have noted erythema of the extremities of these patients. The patients themselves would call it to the doctor's attention. When asked about his hands by another patient, the one demonstrating this sign would answer that it was, "Tb. hands."

This sign consists of a diffuse redness of the palmar surface of the hand. In early cases it starts on the pads of the distal phalanges and spreads to the thenar and hypothenar eminences. Not infrequently it may start on all these points at once. As it advances, it surrounds the entire outer aspect of the palmar surface leaving the centre of the palm pale in comparison. When this sign is marked it extends on the dorsum of the hand around the finger nails to the distal interphalangeal junction.

On the feet, it appears on the plantar surface, involving the pads of the toes, the ball of the foot and along the lateral half of the plantar surface to the pad of the heel. It fades on pressure and color returns immediately on the release of pressure. When present for many years, the erythema takes on a dull purplish hue. The area involved is not warmer than the normal appearing skin.

An increase in the temperature of the atmosphere results in an accentuation of the erythema while a decrease in temperature causes it to become less prominent.

Because this sign involves the capillaries, it would be well to review briefly capillary structure and physiology. According to Wiggers (1) true capillaries consist of only a single layered endothelial tube. Their length averages approximately 0.5 mm. (0.2 mm. to 0.8 mm.) and their diameter may not exceed that of an erythrocyte (extremes 5 to 20 μ in different regions). Each corpuscle or equivalent quantity of plasma remains in the capillaries less than one second. This unfavorable condition for interchange of metabolites is compensated however by the tremendous number of capillaries. The total cross section area of the capillary bed has been variously estimated as between 300 and 800 times that of the aorta (Tigerstedt, Hess). A transverse section of skeletal muscle equal to that of an ordinary pin contains, in addition to 200 muscle fibres, some 700 parallel capillaries and the ratio for heart muscle is still more favorable for capillaries (Wearn and associates). The capillaries in all the muscles of an average man if laid end to end would stretch several times around the earth (Krogh). This gives a large surface for interchange of substances; induced calculations by Krogh indicate that each cc. of blood in the capillaries has a surface exposure of 5,600 square cm. in a dog and it would be even more in man.

Skin color, apart from effects due to pigmentation and variations in thickness of the epidermis, is determined chiefly by its blood supply. The depth of color depends only

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[2] Veterans Hospital, Albuquerque, New Mexico.

to a minor extent upon the number of minute blood vessels per unit surface area, but is conditioned chiefly by the fulness of these vessels in the sub-papillary plexus. Thus, actual counts of capillary loops show that certain regions, such as the palms of the hands, soles of the feet and buttocks, contain a denser arrangement of vessels which may account in part for their naturally redder hue, as shown by Wetzel and Zotterman (2). Using photoelectric methods, Hertzman (3) gives the following order of richness in arterial supply: finger pads, ear lobes, toe pads, palms, forehead, face, dorsum of fingers, hand, foot, skin over forearm, knees and tibia.

The shade of color on the other hand is not an index of circulation rate as is evident, according to Wiggers, from the fact that the areas with deepest color are frequently colder than other paler areas. Extreme differences in blood flow are easily detected by the physician or even the patient through an exceptional coldness or warmth of parts. Minor differences require application of covered thermometers or the use of thermocouples.

The natural differences in skin color are conditioned mainly by the state or tone in the minute vessels. This varies greatly in different areas and even in contiguous areas of the skin. Owing to the continued exposure and consequent stimulation by heat, cold and actinic rays, the capillaries and venules of the face, ears, hands, and to a variable extent, depending on fashion of dress the neck, arms and legs possess less tone than those of more protected regions. Consequently, these regions not only have a naturally redder hue, but their color is affected more by arteriolar vasodilation and constriction.

This probably accounts for the fact, state Lewis and Landis (4), that sudden changes in skin color, for example, the pallor attending nausea and the flushing of emotional blushing, are most noticeable in the face and ears. The vasomotor impulses concerned appear to pass via the cervical sympathetic chain which contains both dilator and constrictor fibres.

The anatomical arrangement of cutaneous blood vessels is such that contiguous areas are not equally well supplied with blood. In consequence, capillaries in neighboring areas are not in equal states of tonic contraction. These differences become noticeable, however, only when arteriolar dilatation occurs, for then the more dilated capillaries fill more completely. This gives the skin a speckled or mottled, rather than a definitely hyperaemic appearance.

In order to further demonstrate the rich circulation in the hand, Abramson and Ferris (5) stated, "At 32°C. it is apparent that, if we disregard any muscle tone, there is almost a three-fold difference in the flow of blood through the skin of the hand as compared to the forearm." Speaking of differences in circulation of the hand and forearm Lewis (6) states, "Anatomically the blood vessels of the skin in these two areas differ in two respects: (*1*) the relative number of skin capillaries and small vessels per unit area is greater in the hand than in the forearm; (*2*) many arteriovenous anastomoses have been found in the palm and fingertips but which, as far as we are aware, are not present in the forearm.',

A group of 23 patients manifesting erythema of hands and feet was studied at the Veterans Hospital in San Fernando, California, in order to determine its probable aetiology. They consisted of middle-aged patients with advanced pulmonary lesions. One did not have a tuberculous infection, but demonstrated this physical sign to a marked degree.

A review of the data obtained in this study follows:

1: Ages varied between thirty-two and sixty-one years.

2: Temperature varied from subnormal to normal range to an elevation of 100°F. in 2 cases in the evening.

3: Pulse rate ranged from 72 to 110 per minute.
4: Respiration rate varied from 20 to 22 per minute.
5: Blood pressures were low on the whole, as would be expected in pulmonary tuberculosis. The lowest being 98/60 and the highest was 142/80.
6: Red blood count and haemoglobin readings were a high normal. One case had a haemoglobin reading of 111 per cent with a normal red blood cell count.
7: Sedimentation rate was markedly increased in 20 patients and slightly increased in 3 patients.
8: Vital capacity was markedly diminished in 21 patients and was somewhat lower than normal in the 2 remaining cases.
9: Operative procedures undergone:

10 patients had never had any thoracic surgery or pneumothorax.
7 patients had pneumothorax of which 4 had been discontinued as unsatisfactory and 3 were still receiving refills.
3 patients had a thoracoplasty.
7 patients had a phrenicotomy.
4 patients had a bronchoscopy.
2 patients had cavity aspiration by Monaldi technique. Several patients had had more than one surgical procedure.

10: Circulation time was determined by the calcium gluconate method, introduced by Goldberg (7), and was found normal in these patients, confirming the observations of Hurst and Brand (8).
11: Pulmonary disease:

21 cases had far advanced lesions.
1 had a moderately advanced lesion.
1 had a nontuberculous empyema, treated by a three-stage thoracoplasty.

Among the substances that cause capillary dilatation, according to Moon (9), are bacterial toxins. In 1891 Bouchard (10) found that Koch's tuberculin caused a dilation of the rabbits retinal vessels which lasted for days.

Haven Emerson (10) in 1911 wrote, "My own experiments on lower animals point to a distinct vasodepressant effect of the tubercle products, the actual manner of such toxic action remaining undetermined, but the indications being that the central rather than the peripheral, the nervous rather than the muscular mechanism of the circulation is the sufferer."

In considering the pathogenesis of this physical sign, it is fairly clear that it is caused by the effect of the bacterial toxin through a systemic action causing a peripheral capillary vasodilatation. This sign appears before clubbing of the fingers makes its appearance, provided it eventually does. It is very easy to observe and I believe it has been overlooked or underestimated. In perusing many textbooks in physical diagnosis and medicine, I have been unable to find mention of it. To me, it signifies pulmonary disability whether due to tuberculosis, emphysema, chronic empyema, chronic bronchitis, bronchiectasis or chronic lung abscess. I have not observed this sign in nonpulmonary patients.

You have seen those heavy, florid, thick-chested persons who have a chronic cough, often smoke excessively, display dyspnoea on slight exertion, breath noisily and who, when they laugh, precipitate a paroxysm of coughing. These people expectorate sputum which at times is semipurulent. They are emphy-

sematous and usually have a superimposed chronic bronchitis or bronchiectasis with consequent impairment of pulmonary function. This type of patient often demonstrates this physical sign.

An interesting problem suggests itself in this condition. Perhaps in addition to the effect of toxins this capillary vasodilatation may be another example of nature's compensatory mechanism. In effect, this would be a means to enhance gaseous exchange through the skin in view of the existing defective pulmonary function. It is hoped that further study may prove or disprove this speculation.

SUMMARY

1. Erythema of the extremities as a physical sign in pulmonary tuberculosis and other pulmonary diseases is described. It consists of a peripheral capillary vasodilatation of the palmar surface of the hands and plantar surface of the feet.

2. A study of 23 patients demonstrating this physical sign to a marked degree was made and its aetiology is revealed as the effect of bacterial toxins through systemic action.

3. The presence of this sign, which is not mentioned in textbooks, denotes pulmonary disability whether due to tuberculosis, emphysema, chronic bronchitis, chronic empyema, bronchiectasis or chronic lung abscess.

4. This capillary vasodilatation raises the question that it may be, in addition to the effect of toxins, another example of nature's compensatory mechanism to aid in further gaseous exchange through the skin in view of the defective pulmonary function.

SUMARIO

1. Descríbese el eritema de los miembros como signo físico en la tuberculosis pulmonar y en otras afecciones pulmonares. Consiste en vasodilatación capilar periférica de la palma de las manos y planta de los pies.

2. Un estudio de 23 pacientes con marcada acentuación de este signo físico, reveló que era ocasionado por toxinas bacterianas que afectaban el organismo.

3. La presencia de este signo, no mencionado en las obras de texto, denota incapacidad pulmonar, debida a tuberculosis, enfisema, bronquitis crónica, empiema crónico, bronquiectasia o absceso pulmonar crónico.

4. Esta vasodilatación capilar suscita la cuestión de si representa, además del efecto de las toxinas, otro ejemplo del mecanismo compensador de la naturaleza para fomentar el intercambio gaseoso por la piel, dada la disfunción pulmonar.

I acknowledge, with gratitude, the coöperation and encouragement of Dr. J. J. Beatty, my Clinical Director.

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THE FUNCTIONAL CAPACITY OF THE CONTRALATERAL LUNG[1, 2, 3]

WALTER K. WHITEHEAD, NEWTON WHITMAN AND BERNARD SHACTER

Two factors of practical significance in the application of collapse therapy can be determined by a study of the respiratory function of each lung separately. One of these is the division of the circulating blood between the lungs. The other is the distribution of the ventilated air over the capillary bed of each lung.

In the absence of anoxaemia, the oxygen intake of a lung varies with its circulation. The percentage of the total oxygen absorbed by one lung is roughly equal to the percentage of the total blood flow passing through that lung. Thus, measurement of the oxygen intake of the individual lungs is really a measurement of the relative blood flow.

The circulation and ventilation of one of the lungs may be greatly reduced in pulmonary tuberculosis. Circulation may be reduced more than ventilation, and ventilation more than circulation, in different parts of the same lung. Areas of lung tissue which are poorly ventilated in relation to the amount of blood flowing through them are actual or potential sources of arterial anoxia. In this discussion the term "underventilation" will be used in a relative sense, indicating that the ventilation of an area is inadequate in terms of the amount of blood perfusing it.

The presence of underventilated tissue is indicated by a low oxygen content of the arterial blood during exercise or while breathing a low oxygen mixture. When it is known that some of the lung tissue is underventilated, it is important to know how much of that underventilated tissue is in the contralateral lung. For if the contralateral lung contains underventilated tissue, it cannot be expected to carry on adequate gas exchange after most of the blood from the collapsed lung has been shunted through it.

The oxygen content of the blood passing through underventilated tissue is not raised as high as that of blood perfusing well ventilated tissue, unless atmospheres unusually rich in oxygen are inspired. This means that the amount of oxygen absorbed through underventilated tissue in a given time is less than it would be if the ventilation were adequate for the size of the capillary bed and the minute volume of blood flow. The failure of oxygen absorption is not marked at rest and while breathing air, and it is entirely absent while breathing high oxygen mixtures, unless some of the lung tissue is isolated from the ventilating air by bronchiolar obstruction. On the other hand, this failure of oxygen absorption by underventilated tissue is greatly exaggerated while breathing a low oxygen mixture.

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[2] From the Wm. H. Maybury Sanatorium (The Detroit Municipal Tuberculosis Sanatorium), Northville, Michigan, and The Herman Kiefer Hospital, and the Department of Medicine, Wayne University, College of Medicine, Detroit.

[3] Aided by a grant from the McGregor Fund of Detroit.

This fact makes it possible to demonstrate the presence or absence of underventilated tissue in either one or both lungs. With the airway to each lung separated by a Gebauer or a Zavod catheter, one lung at a time can be given a low oxygen mixture to breathe with the other lung breathing air, or both lungs can inspire first air and then the same low oxygen mixture during the same period. Both of these procedures have been used and each has its advantages. The gas exchange and ventilation of each lung were determined by the open circuit method.

Case 1: A white male, aged twenty-eight, was admitted in 1940 with far advanced pulmonary tuberculosis. The infiltration of the right lung extended from the apex to the fifth anterior rib and tenth vertebral spine with multiloculated cavities below the clavicle. The disease in the left lung was approximately the same in extent and intensity with a large oval cavity near the centre of the lung field. Artificial pneumothorax was begun

TABLE 1

LUNG	INSPIRED GAS	O_2 INTAKE			CO_2 OUTPUT			MINUTE VOLUME		RESPIRATORY QUOTIENT
	% O_2	*cc./min.*	*cc./lit.*	%	*cc./min.*	*cc./lit.*	%	*Lit./min.*	%	
Right	21	233	34	81	227	34	81	6.78	76	0.97
Left	21	55	26	19	53	25	19	2.13	24	0.97
Total		288	32		280	31		8.91		0.97
Right	16	186	34	68	180	33	83	5.50	78	0.97
Left	21	87	35	32	37	23	17	1.57	22	0.42
Total		273	39		217	31		7.07		0.80
Right	21	331	64	94	189	37	74	5.15	69	0.57
Left	16	21	9	6	67	29	26	2.28	31	3.20
Total		352	47		256	34		7.43		0.73

on the left, but found to be ineffective. Complete reëxpansion had occurred within three months after induction but not without moderate pleural thickening and slight retraction to this side. Pneumothorax was maintained on the right side for nine months, but lost during the treatment of a traumatic pneumothorax which followed pneumonolysis. This pneumothorax did not result in much pleural thickening. The cavity in the right lung had disappeared but the large cavity in the left lung persisted and thoracoplasty was thought necessary to bring about healing.

The data found during catheterization are given in table 1. The distribution of blood flow is indicated by the apportionment of oxygen absorption during the first period.

There was a progressive increase in total oxygen absorption in relation to total ventilation during the three periods of observation, which accounts for the lack of reduction in the oxygen absorbed per liter by the right lung when it was ventilated by 16 per cent oxygen, but in spite of this there was marked failure in this function by the left lung under corresponding conditions. At the same time, there was an increase in the carbon dioxide excretion per liter of ventilation by the left lung as well as by the right. The marked elevation of the respiratory quotient, as well as several other factors in the table,

lend weight to the conclusion that the left lung fails to absorb oxygen in proportion to its blood flow and that it would thus be a potential source of anoxaemia during the increased blood flow which accompanies exercise. The response of the left lung during catheterization, as indicated by the respiratory quotient and oxygen absorption per liter of ventilation, was good while the lung breathed air. In evaluating this response, it is necessary to consider it in relation to the fraction of the total blood flowing through it. The carbon dioxide output, in cubic centimetres per minute and cubic centimetres per liter, suggests that the relative blood flow was approximately the same during the second period as it was during the first.

Breathing a low oxygen mixture by one lung lowers the oxygen content of both the arterial and venous blood. The venous blood is, of course, oxygenated to a higher degree in flowing through the lung breathing air than through the lung breathing a low oxygen mixture. The oxygen intake in cubic centimetres per liter is evidently related to the pulmonary venous-mixed venous oxygen difference. The arteriovenous carbon dioxide difference likewise should vary with carbon dioxide output in cubic centimetres per liter in a similar manner, and from these values in the third period it may be inferred that the rather pronounced increase in total oxygen absorption (tissue utilization) was accomplished for the most part by an increase in the pulmonary venous-mixed venous oxygen difference of the right lung. Anoxic blood from the left lung could well be one of the factors producing this change.

Thus it would seem that the right lung carried the largest portion of the blood flow and was capable of more efficient gas exchange than the left.

An additional factor which should be kept in mind throughout all tests of this kind is the effect of the drugs used in preparation for the application of cocaine prior to the introduction of the catheter. We have repeatedly observed slight to moderate cyanosis while breathing a low oxygen mixture in patients who displayed no such sign without the drugs—in our case morphine and scopolamine preceded by a barbiturate.

This anoxia must, therefore, be due to depression of respiration by the sedative drugs with a resultant relative underventilation. Such a hypothesis is supported by the fact that the arterial oxygen saturation has been found higher in the same person without drugs while breathing a low oxygen mixture with both lungs than with drugs and with the catheter in place while breathing the same low oxygen mixture with only one lung, the other lung breathing air.

Wright and Woodruff (1) have shown that the introduction of the catheter lowers appreciably the oxygen saturation of the arterial blood, even while breathing an atmosphere as rich in oxygen as room air. As they point out, misplacement of the catheter in such a way as to block some of the lung tissue would produce an unusually low arterial oxygen saturation. We feel, however, that even in abnormal persons the saturation of the blood can be so readily raised to a normal level by purely neurogenic overbreathing and that it can be lowered so greatly by drugs which depress respiration that it is difficult to rely on arterial blood gas analysis as a test of the position of the catheter. Instead, for this purpose, we rely on a careful bronchoscopic examination during which

the length of the left main bronchus between the carina and first tributary and the presence or absence of a right upper lobe bronchial orifice in the trachea are noted. The catheter can then be placed with considerable confidence under fluoroscopic control.

Case 2: A forty-seven year old white male was admitted with far advanced pulmonary tuberculosis. There was soft infiltration of the upper two-thirds of each lung and small cavities in both lungs below the clavicles. Simultaneous bilateral pneumothorax was instituted and maintained without complications on the right for eight months and on the left for twenty months. There appeared to be, at the time the respiratory studies were done, slight pleural thickening on the left with very slight retraction to this side and little or no definite pleural change on the right. Thoracoplasty was contemplated because of a persistent cavity on the right. There had never been any dyspnoea.

The results of catheterization in case 2 are given in table 2. The oxygen intake of the left lung, in cubic centimetres per liter of gas inspired, fell during the period in which both lungs breathed 16 per cent oxygen at the same time. This means that the ventilation of this lung was greater in relation to the volume of oxygen actually absorbed through

TABLE 2

LUNG	INSPIRED GAS	O_2 INTAKE			CO_2 OUTPUT			MINUTE VOLUME		RESPIRATORY QUOTIENT
	% O_2	*cc./min.*	*cc./lit.*	%	*cc./min.*	*cc./lit.*	%	*Lit./min.*	%	
Right	21	158	51	60	121	39	67	3.09	67	0.77
Left	21	94	61	40	60	39	33	1.53	33	0.64
Total		252	55		181	39		4.62		0.72
Right	16	211	56	75	157	42	74	3.77	70	0.74
Left	16	69	42	25	55	33	26	1.65	30	0.80
Total		280	52		212	39		5.42		0.76

it than it was while both lungs breathed air. Yet the oxygen absorption of the left lung fell during the low oxygen period while that of the right lung rose.

There was, perhaps, some slight cyanosis while breathing air with the catheter in place, and definite cyanosis of moderate degree while breathing low oxygen under identical conditions and without interference with the catheter or detectable change in its position. The saturation of the arterial blood under basal conditions without drugs and breathing the same low oxygen mixture on another day was not abnormally reduced and there was no cyanosis. This appears to be an instance of depression of respiration by sedative drugs. The net effect is that of reducing the oxygen content of the inspired gas to a level lower than 16 per cent. The data indicate that thoracoplasty on the right would greatly increase the burden of an inefficient left lung.

An explanation of the observed effect of breathing low-oxygen mixtures is given in figure 1, which shows the relationship between the amount of oxygen in the arterial blood expressed in percentage saturation of the haemoglobin (and in volumes per cent oxygen content when the oxygen capacity is 20 volumes per cent), and the amount of oxygen in the alveolar air of the lungs, expressed as the partial pressure of oxygen in mm.Hg. The point at which the line r crosses the

curve indicates the oxygen saturation of blood leaving a well ventilated area of lung tissue. Here the alveolar oxygen tension is about 100 mm.Hg. The point at which the line l crosses the curve represents the saturation of blood leaving a poorly ventilated area of lung tissue. Here the alveolar oxygen tension is only 70 mm.Hg because the air in such an area remains in contact with the capillary blood long enough to permit more oxygen to be removed from it. If the volume of blood flowing through the two areas is the same, the saturation of the mixed arterial blood would be indicated by the point s, where the horizontal coördinate half way between those of r and l crosses the curve. If the alveolar oxygen tension were lowered 40 mm.Hg by breathing a low oxygen mixture, the saturation of the blood leaving the well ventilated area would fall on the curve where the line r′ crosses it. Similarly the blood from the poorly ventilated area would

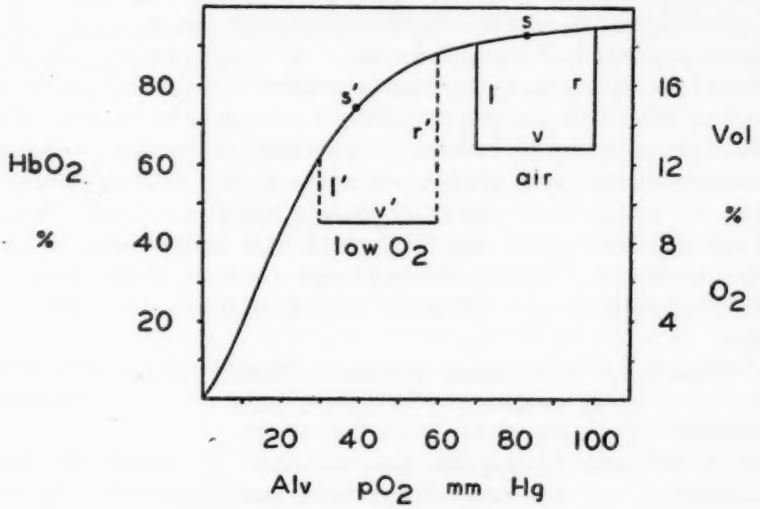

FIG. 1

be saturated to the point indicated by the intersection of the line l′. Then s′, arrived at as above, would show the saturation of the mixed arterial blood. If all the lung tissue were well ventilated the arterial oxygen saturation would be where r′ meets the curve. Therefore s′ indicates the presence of underventilated tissue in the lungs which, because of the flat, upper portion of the curve and the relatively high oxygen tension of the alveolar air while breathing atmospheric air at sea level, would not be apparent under ordinary conditions.

The effect of giving a low oxygen mixture to the lungs, the blood flow through each of which is equal, with the double bronchial catheter in place, can be visualized by regarding the line r as the pulmonary venous-mixed venous oxygen difference of the right lung breathing air, and l, the corresponding value of the left lung; l′ and r′ indicate the same values of the same lungs breathing a low oxygen mixture. The right lung here is well ventilated, while the left contains much underventilated tissue. The saturation of the mixed arterial blood is

indicated by s and s′ and the horizontal coördinates v and v′ indicate the oxygen content of the mixed-venous blood. The total blood flow (cardiac output) is assumed to be constant and the arteriovenous oxygen difference is the same (about 58 cc. per liter of blood) during both periods. Thus, a total blood flow of four liters per minute would mean that the total oxygen absorption is $4 \times 58 = 232$ cc. per minute and that oxygen absorption is divided between the lungs in proportion to the heights of the lines r and l while breathing air, and r′ and l′ while breathing low oxygen. Thus $r + l = r' + l'$. It is apparent that the defect in the oxygen absorbing ability of the left lung, due to its content of vitiated alveolar air, is exaggerated by breathing a low oxygen mixture.

DISCUSSION

It is obvious that obliteration of some of the pulmonary capillaries must result in the overloading of other capillaries or in the opening up of new capillaries, if the cardiac output remains the same. The work of Wearn (2), Hurtado (3) and their associates offers experimental evidence for the statement that the cross-sectional area of the pulmonary capillary bed can be increased. The focal character of the pathological changes in pulmonary tuberculosis suggests that some of the blood must be shunted into healthier areas. Since it does not seem likely that the ventilated air can be accurately and proportionally distributed through the circulated areas, this must mean that circulation is in excess of ventilation in some parts of many diseased lungs. It is also likely that distortion of bronchioles might impair ventilation in areas in which the capillary bed is still intact.

Other evidence (4, 5, 6, 7) of disproportion between circulation and ventilation lies in the demonstrable variations in the oxygen content of different portions of a single expulsion of alveolar air.

Cournand, Richards, Darling and their associates (8, 9) have demonstrated poor distribution of the ventilated air by several methods and they have further shown (10) that air may stagnate in areas which have but little circulation, as well as in areas perfused by an amount of blood which is excessive in relation to the ventilation of the part.

If other evidence were needed it could be found in the fact that anoxaemia does develop in some tuberculosis patients when they exercise (11, 12) and when they breathe a low oxygen mixture (13, 14). For the only manner in which anoxemia can be produced is by relative underventilation of some of the perfused tissue or by the existence of a barrier to the diffusion of gases across the alveolar and capillary walls. There is excellent evidence of focal relative underventilation but little or no compelling evidence for the barrier theory.

The pulmonary ventilation of tuberculosis patients, including those in whom respiratory impairment is manifest, is, in the majority of cases, within the normal range of variation when it is expressed in terms of square metres of body surface. When it is expressed in relation to the minute volume of oxygen absorption, however, it is nearly always increased. Here we have, then, a disease of the lungs in which anoxaemia occurs in the face of a normal or exces-

sive pulmonary ventilation. It would be difficult indeed to explain this on any ground other than focal relative underventilation.

The manner in which underventilated areas contribute detectable amounts of anoxaemic blood to the general circulation during low oxygen breathing is demonstrated in figure 1. The arterial anoxia which develops during exercise in certain abnormal subjects can be explained in the same way; for the lungs occupy an intermediate position in the transfer of oxygen from the external environment to the pulmonary arterial blood. In one case the supply of oxygen is diminished and in the other the demand for oxygen is increased. To put it another way, an underventilated area must supply an increased amount of oxygen at an accelerated rate to a larger volume of blood in order to avoid arterial anoxaemia during physical activity.

The functional status of the contralateral lung should, as a general rule, be investigated during and after the fifth decade of life. When the contralateral lung is partially collapsed or when there is evidence of, or a history suggesting extensive previous disease of either parenchyma or pleura, the impairment of function may be greater than one would expect from the X-ray and clinical appearance of the patient. When the contralateral lung has reëxpanded following artificial pneumothorax, gas exchange may well be either better or worse than anticipated. Other indications arise in the course of practice.

It must be borne in mind that catheterization of the bronchi affords a means of testing the function of one lung as compared to that of the other at a given time. When the function of both lungs is equally impaired by a diffuse lesion, the response, as far as gas exchange is concerned, is the same as it would be if both lungs were normal, because pulmonary disease does not in itself reduce oxygen consumption.

It is therefore necessary to interpret results in terms of general respiratory efficiency as determined by other means. The lung which has the greatest blood flow will, of course, absorb most of the oxygen used by the tissues. But when the existence of underventilated tissue has been demonstrated, the success or failure of collapse therapy may depend on knowing whether this potential source of anoxaemia is in the lung to be collapsed or in the other lung. If blood is shunted from an underventilated lung into a well ventilated lung, respiratory function may improve; if it is shunted into a lung containing underventilated tissue, the disability may be increased. It is sometimes possible to collapse the lung which has the greatest blood flow, but, so far at least, it has not seemed wise to place a greater burden on a contralateral lung which already shows evidence of respiratory failure under stress.

SUMMARY

The data obtained by bronchial catheterization of 2 patients were presented as an illustration of the kind of information to be gained by this procedure when it is carried out in open circuit. The total gas exchange of each lung was determined, breathing air and a low oxygen mixture. In one case, both lungs breathed air simultaneously, and then one at a time breathed low oxygen while the other

breathed air. In the other case, both lungs breathed air and then the low oxygen mixture simultaneously.

It was pointed out that the fraction of the total blood flow passing through each lung is the same as the fraction of the total oxygen absorption which enters the blood stream through each lung, when atmospheres containing enough oxygen to prevent arterial anoxia are inspired. In other words, relative oxygen absorption is equal to relative blood flow under ordinary conditions. Failure of oxygen absorption on the part of either lung suggests that ventilation is not proportional to circulation in part of that lung. This disturbance has been described as inefficient mixing of the inspired air with the alveolar air which, by reason of varying duration of contact with pulmonary capillary blood, is of variable composition in different parts of certain lungs. Such changes are not notable while air is breathed at rest in low altitudes, but they are readily recognizable when low oxygen mixtures are breathed or during physical activity. An explanation of the physiological mechanisms involved was described graphically on the basis of the relationship between the partial pressure of oxygen in the alveolar air and the percentage of oxyhaemoglobin in the arterial blood.

The effect of sedative drugs, placement of the catheter and the pathological physiology involved in the interpretation of results were discussed.

SUMARIO

Preséntanse los datos obtenidos por el cateterismo bronquial de 2 enfermos como ejemplo de la clase de información que permite obtener este procedimiento cuando se lleva a cabo en circuito abierto. Se determinó el cambio total de gas de cada pulmón haciendo aspirar aire y una mezcla baja en oxígeno. En un caso ambos pulmones recibieron aire simultáneamente y luego uno la mezcla escasa en oxígeno mientras el otro inhalaba aire. En el otro caso, ambos pulmones inhalaron simultáneamente primero aire y luego la mezcla pobre en oxígeno.

Hácese notar que la fracción de la circulación sanguínea total que atraviesa cada pulmón es idéntica a la de la absorción total de oxígeno que penetra en la circulación a través de cada pulmón cuando se inhalan atmósferas que contienen suficiente oxígeno para impedir la anoxia arterial. En otras palabras, la relativa absorción de oxígeno es igual a la circulación sanguínea relativa en condiciones ordinarias. La falta de absorción de oxígeno de parte de uno u otro pulmón indica que la ventilación no es proporcional a la circulación en parte de dicho pulmón, habiéndose descrito dicho trastorno como debido a una mezcla ineficaz del aire inhalado con el alveolar, el cual, por razón de la variable duración del contacto con la sangre de los capilares pulmonares, reviste una composición variable en diversas partes de ciertos pulmones. Esos cambios no son notables mientras se respira aire en descanso en sitios poco elevados, pero son fáciles de reconocer cuando se inhalan mezclas pobres en oxígeno o durante la actividad física. La explicación de los mecanismos fisiológicos que intervienen es descrita gráficamente, tomando por base la relación entre la presión parcial de oxígeno en el aire alveolar y el porcentaje de oxihemoglobina en la sangre arterial.

Discútense el efecto de los sedantes, la colocación de la sonda y la patofisiología que intervienen en la interpretación de los resultados.

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DISCUSSION

Dr. Andre Cournand, New York, New York: The presentation of Doctor Whitehead is a tribute to the soundness of his physiological thinking. The method he proposes offers a new means of approach to the study of the correlation between ventilation and circulation in a diseased lung.

Up to date, two methods, largely experimental, have been used to determine the proportion of blood circulating through each lung. The first method was developed by R. L. Moore in dogs, later applied to man by Bruce and Jacobaeus, and more recently studied by Wright and Woodruff. It necessitates the breathing of an atmosphere rich

in oxygen by one lung, while the other lung breathes an atmosphere totally deprived of oxygen. If one makes an assumption regarding the degree of oxygen saturation of the mixed venous blood (which is in normal subjects about 60 to 70 per cent saturated with oxygen) and determines arterial oxygen saturation, a simple calculation gives a fairly good estimate of the percentage of blood circulating through each lung. We have used this method in a fairly large number of subjects and have come to the conclusion that the risk entailed by inducing an acute degree of anoxia even for a short period of time is not justified by the results obtained. The second method is much simpler and gives information just as accurate, as we were able to demonstrate in patients studied by both methods. It is based on the rebreathing of pure oxygen by both lungs and comparing the slope of the recorded curve of oxygen absorption. Uneven distribution being eliminated by breathing an atmosphere rich in oxygen for a sufficiently long period of time, the chief factor that determines the slope of the curves of oxygen absorption is circulation.

Both methods, however, do not answer the important question as to the degree of correlation between ventilation and circulation in each lung separately. It appears that Doctor Whitehead's new technique should give an answer to the problem. It is, of course, important to realize that low oxygen breathing does not reproduce normal physiological conditions, and certainly its effects cannot be compared with that of exercise. During the latter, both circulation and ventilation increase in variable proportions; in the former the concentration of oxygen is lowered, but ventilation and circulation apparently do not increase, at least during the test. It should be mentioned in this regard that patients with chronic pulmonary emphysema, if transported to an altitude of 6,000 feet, suffer a more or less severe degree of anoxia, and yet at sea level, breathing room air and performing a moderate type of exercise, they may still have a perfectly normal arterial oxygen saturation.

Before closing, I should like to suggest that, as a rule, the simple method of recording volumes and oxygen consumption of each lung separately in a closed circuit apparatus of the Collins type, as originally used by Jacobaeus *et al.* and illustrated recently in this country by Pinner *et al.*, is for practical purposes sufficient. The open circuit method offers decided advantage over the closed circuit, if and when the type of respiration is very irregular, so that no oxygen slope can be determined. This belief is based on an experience of over two years, during which all known techniques (open circuit, closed circuit, nitrogen block, etc.) were being compared on the same subjects. A great deal of valuable information of physiological interest has been accumulated and at the same time an unprejudiced estimate of the clinical value of the various techniques so far proposed could be made.

Dr. Max Pinner, New York, New York: Doctor Whitehead's paper is a logical development of his former work. He has shown previously that breathing oxygen of reduced tension is a valid functional test with the special advantage, over exercise tests, that the functional capacity of the lung is tested, as much dissociated from the cardio-vascular function as is probably possible. Such specific organ tests are, of course, of great significance, but it may be pointed out that in practical application they have definite limitations, since, after all, we must know the patient's functional capacity and not only the functional capacity of his lung.

In Doctor Whitehead's presentation of to-day a most important problem was attacked: the functional capacity of the contralateral lung. His method is designed to detect whether or not the contralateral lung as a whole or in part shows a disproportion between

ventilation and pulmonary circulation, leading to insufficient arterialization, or in his own expression, it detects hypoventilation, relative to circulation. It seems to me that the method does not exactly detect hypoventilation, if one adheres to strict definition of ventilation, namely, the amount of air breathed in and out per time unit. It does detect deficiency in oxygen absorption which may be due to hypoventilation, but is probably more frequently caused by a poor mixture of alveolar air, as in emphysema, and interference with oxygen absorption, as in fibrosis, because the diffusing membrane is thickened and, therefore, less permeable for oxygen. A disproportion between ventilation and oxygen absorption in *one* lung is indicated by a high ventilation equivalent, which is usually associated with hypoventilation of that lung, but may be associated with hyperventilation, particularly in cardiacs. This in itself suggested that a clear-cut dissociation of pulmonary and cardiac function is, in the last analysis, impossible. It should further be pointed out that Doctor Whitehead's method will detect deficient oxygen absorption only if the damaged part of the lung contains sufficient pulmonary circulation, so that its underarterialization is still detectable after it has been mixed with the well oxygenated blood from other parts of the two lungs. The method would, therefore, not detect any abnormality if practically no pulmonary circulation existed in the involved portion of the lung. However, these are natural limitations of the applicability of Doctor Whitehead's method, of which he is undoubtedly well aware. They are pointed out only to specify the indication for this particular procedure and to emphasize that no one single test *per se* can be sufficient for the correct estimation of functional respiratory capacity. The test presented appears to be a significant addition to functional tests if it is used with the awareness of its proper application and limitation and in conjunction with other functional tests. Finally, I should like to ask Doctor Whitehead whether bronchospirometry with reduced oxygen tension has detected many times deficiencies not indicated by bronchospirometry with normal oxygen tension. I ask this, because it is evident to us that bronchospirometry *per se* does not measure basal function; it is in itself an exercise test.

COLLAPSE THERAPY

Trends in Frequency and Type of Surgical Procedures in the Treatment of Pulmonary Tuberculosis[1]

A Statistical Review of Institutional Experience during the Five-Year Period 1937-1941

GODIAS J. DROLET[2]

Part I

Collapse Therapy

This study was undertaken to determine, first, the extent to which collapse procedures are used at the present time in the treatment of pulmonary tuberculosis, second, the general mortality ratio of in-patients of tuberculosis hospitals and sanatoria. There was likewise borne in mind the general desire to ascertain local practices. For practical purposes, it was decided to consider only large institutions or hospital services, generally of three hundred beds or more, and to confine the study to patients therein, since fairly complete records were more likely to be available than if such an investigation were attempted among ambulant patients treated at clinics or in private medical practice. The present survey is based upon special reports, for each of the five years from 1937 to 1941, received from 101 of the larger Canadian and American tuberculosis hospitals and sanatoria[3] with a total rated capacity, in 1938, of 33,050 beds for adult patients (table 1). For completeness, only 99 schedules could finally be utilized. The data with regard to collapse therapy were limited to adult patients, since it is primarily among them that active pulmonary disease is more likely to demand this form of treatment. This choice made it possible to eliminate debatable cases of childhood type of tuberculosis.

During the period 1937–1941, in the 101 institutions mentioned, 252,704[4] patients, adults and children,[5] were treated, of which 218,723 were discharged, alive or dead, and there still remained under treatment on December 31, 1941, 35,430 patients of all types.

REGIONAL DIVISIONS

The reports and their details, because of interest from a regional aspect, were subdivided, in order to bring out local practices, and regrouped into nine sections with a certain number of institutions as follows: Canadian, eleven; New Eng-

[1] An address before the American College of Chest Physicians, Eighth Annual Meeting, Atlantic City, June 7, 1942.

[2] Consulting Statistician, Tuberculosis Sanatorium Conference of Metropolitan New York.

[3] See list at end of paper.

[4] The magnitude of this host of sufferers in only one-third of the tuberculosis beds in Canada and the United States is still but a fraction of the ravages of the "White Plague" even nowadays, since it ignores the larger number of ambulant patients attending public clinics or under care of private physicians.

[5] Exclusive of those in preventoria.

land, six; New York City, ten; upstate New York, thirty-two; New Jersey, seven; Mid-Atlantic and Southern, nine; Central Inland, seven; Northern Midwest, eleven; Western, eight (table 1).

Occasionally, the reporting institutions did not have available complete reports of the volume of collapse therapy work for certain years. In such instances estimates were made from the trend already indicated by the figures in succeeding or preceding years, the assumption being that there was a continued similarity in the work at the particular level of the respective institutions; this step was necessary in order to complete a presentation of the situation by regions. Fortunately, for the year 1938, it was frequently possible to provide missing data especially with regard to patient-census, or mortality in institutions, from reports already published by the Council on Medical Education and Hospitals of the American Medical Association.

TABLE 1

Patient-census, bed capacity, ratio of occupancy in 101 tuberculosis hospitals and sanatoria on December 31, 1938, for adults only

SECTIONS	PATIENT CENSUS	BED CAPACITY	OCCUPANCY
			per cent
Canadian (11)	3,393	3,988	85
New England (6)	2,133	2,365	90
New York City (10)	3,951	3,539	112
Upstate New York (32)	3,824	4,062	94
New Jersey (7)	2,089	2,116	99
Mid-Atlantic, Southern (9)	4,589	4,468	103
Central Inland (7)	3,356	3,431	98
Northern Midwest (11)	5,601	6,201	90
Western (8)	2,969	2,880	103
All sections (101)	31,905	33,050	97

BED OCCUPANCY

In 1938, as already stated, the bed capacity for adult patients in these 101 institutions totalled 33,050 and, on the last day of the year, there were accommodated therein 31,905 adult patients, indicating a ratio of occupancy of 97 per cent. The utilization of tuberculosis institutions varied somewhat in the sections surveyed, though in general, except in Canada, New England and certain parts of Northern midwest, the beds available were all taken up for tuberculosis patients by a greater proportion than is usually deemed proper for efficient, economical management and good care.

The Canadian institutions reported an average bed occupancy of 85 per cent of capacity. Among American institutions, the lowest ratio of occupancy at that time, 90 per cent, was in the New England group, particularly in Massachusetts. New York City, with obviously inadequate provision of tuberculosis beds, reported an average of 112 patients per space normally required for 100.

The Mid-Atlantic and Southern group of institutions, taking in the Maryland State sanatoria, that of Washington, D. C. and Oteen in North Carolina, all showed crowding beyond capacity, the ratio of occupancy averaging 103 per cent. In the Western group, the institutions were practically all filled and the greatest overcrowding was in the Los Angeles area, the ratio of occupancy for the entire section also rising there to 103 per cent of normal capacity.

During the period studied, the adult patient-census of the 101 hospitals and sanatoria rose from a total of 31,105 at the end of the year 1937 to 33,225 by the end of 1941 (table 2). This was an increase, for the entire group, of 2,120 adult patients, or of 7 per cent. The situation varied somewhat in different sections, though increases were noted in six of the nine regions. In the Canadian institutions the number of patients for the dates just mentioned rose by 13 per

TABLE 2

Adult patient-census on December 31, 1937-1941, at 101 Canadian and American tuberculosis hospitals and sanatoria

SECTIONS	ON LAST DAY OF YEAR					CHANGE
	1937	1938	1939	1940	1941	1941/1937
Canadian (11)	3,225	3,393	3,562	3,642	3,654	+429 = 13%
New England (6)	2,147	2,133	1,985	1,962	2,046	−101 = 5%
New York City (10)	3,732	3,951	3,993	4,275	4,134	+402 = 11%
Upstate New York (32)	3,771	3,824	3,846	3,772	3,703	−68 = 2%
New Jersey (7)	1,992	2,089	2,152	2,150	2,059	+67 = 3%
Mid-Atlantic, Southern (9)	4,510	4,589	4,713	4,866	5,272	+762 = 17%
Central Inland (7)	3,145	3,356	3,543	3,497	3,484	+339 = 11%
Northern Midwest (11)	5,630	5,601	5,517	5,577	5,458	−172 = 3%
Western (8)	2,953	2,969	3,067	3,143	3,415	+462 = 16%
All sections (101)	31,105	31,905	32,378	32,884	33,225	+2,120 = 7%

cent. In the Mid-Atlantic and Southern section the group of nine institutions saw their adult census increase from 4,510 to 5,272, or by 17 per cent.

It is to be remembered that increases of patient-census reflect not only a greater demand for institutional care but also, occasionally, additions to facilities in the community as well. The factor of a change in available institutions was, however, not necessarily the one present here when there was a decrease reported in the patient-census. In the New England group of institutions, for instance, the patient-census, during the five years studied, fell by 5 per cent, and in upstate New York by 2 per cent, primarily because of the material decline of tuberculosis there lately and the comparative plethora of beds available. In New York City, the census rose by 11 per cent; in New Jersey, it increased by 3 per cent; in the Central inland section, it went up by 11 per cent; and, in the Western group, by 16 per cent, the latter change being due particularly to the larger number of military patients now cared for at the Fitzsimons General Hospital in Denver.

EXTENT OF COLLAPSE THERAPY

On December 31, 1937, in 99 of the Canadian and American institutions surveyed, there was a total of 30,580 adult patients (table 3, part I). On that same date, it was reported that 14,992 adult patients were under some form of collapse therapy (table 3, part II). At the end of 1938, the number of patients under any form of collapse therapy rose slightly to 15,547. On December 31, 1939, this time in 100 institutions with a patient-census of 32,002, those under collapse numbered 16,451 and a crest was reached in the number of patients receiving this form of treatment. At the end of 1940, in the same 100 institutions, there had been a slight recession and the patients under collapse therapy numbered 16,341; and, by the end of 1941, this was down slightly further to a total of 15,791.

TABLE 3, Part I

Adult patient-census on December 31, 1937-1941 at 99 to 100 Canadian and American tuberculosis hospitals and sanatoria

SECTIONS	CENSUS ON LAST DAY OF YEAR				
	1937	1938	1939	1940	1941
Canadian	3,225	3,393	3,562	3,642	3,654
New England	2,147	2,133	1,985	1,962	2,046
New York City	3,732	3,951	3,993	4,275	4,134
Upstate New York	3,771	3,824	3,846	3,772	3,703
New Jersey	1,992	2,089	2,152	2,150	2,059
Mid-Atlantic, Southern	4,510	4,589	5,030	5,252	5,663
Central Inland	2,852	3,019	3,193	3,209	3,210
Northern Midwest	5,630	5,601	5,517	5,577	5,458
Western	2,721	2,732	2,724	2,795	3,060
All sections	30,580	31,331	32,002	32,634	32,987
Number reporting	(99)	(99)	(100)	(100)	(100)

For all sections, it is seen therefore that first in 1937 (table 3, part III) there was an average of 49 per cent of all the adult patients treated by collapse; and that, at the end of 1941, this was down by one per cent only to 48, there having been reached apparently a period of stabilization from the crest attained in 1939, when the proportion averaged 51 per cent.

The use of collapse therapy by the end of 1941 was least among the New York City group of institutions, where only 30 per cent of the patients were under this type of treatment. This low rate was followed by those in the Central inland section, 39 per cent. The greatest frequency of collapse therapy was found in the Western group of institutions where it averaged 58 per cent.

In six of the regions where a decline was noted (Canadian, New York City, upstate New York, New Jersey, Central inland, Northern midwest), the greatest decrease between 1937 and 1941 in the use of collapse therapy was among the New York City group of institutions studied, where the ratio fell from 43 per

cent to 30 per cent—a decrease of 13 points. In three sections (New England, Mid-Atlantic and Southern, Western) an increase instead was reported.

There were, of course, material variations as to the extent of collapse therapy in individual institutions. In New York City, for instance, where on December

TABLE 3, Part II

Number of adult patients under collapse therapy on December 31, 1937-1941, at 99 to 100 Canadian and American tuberculosis hospitals and sanatoria

SECTIONS	UNDER COLLAPSE TREATMENT ON DECEMBER 31				
	1937	1938	1939	1940	1941
Canadian	1,827	1,973	2,114	2,160	1,947
New England	1,114	1,345	1,188	1,049	1,084
New York City	1,593	1,391	1,384	1,494	1,235
Upstate New York	1,982	1,901	2,038	1,812	1,857
New Jersey	1,126	1,146	1,217	1,146	1,034
Mid-Atlantic, Southern	1,391	1,555	2,106	2,369	2,721
Central Inland	1,176	1,237	1,336	1,405	1,266
Northern Midwest	3,241	3,373	3,525	3,278	3,049
Western	1,472	1,626	1,543	1,628	1,778
All sections	14,922	15,547	16,451	16,341	15,791
Number reporting	(99)	(99)	(100)	(100)	(100)

TABLE 3, Part III

Proportion of adult patients under collapse therapy on December 31, 1937-1941, at 99 to 100 Canadian and American tuberculosis hospitals and sanatoria

SECTIONS	ON LAST DAY OF YEAR					CHANGE
	1937	1938	1939	1940	1941	1941/1937
Canadian	57%	58%	59%	59%	53%	Dec. 4%
New England	52%	63%	60%	53%	53%	Inc. 1%
New York City	43%	35%	35%	35%	30%	Dec. 13%
Upstate New York	53%	50%	53%	48%	50%	Dec. 3%
New Jersey	57%	55%	57%	53%	50%	Dec. 7%
Mid-Atlantic, Southern	31%	34%	42%	45%	48%	Inc. 17%
Central Inland	41%	41%	42%	44%	39%	Dec. 2%
Northern Midwest	58%	60%	64%	59%	56%	Dec. 2%
Western	54%	60%	57%	58%	58%	Inc. 4%
All sections	49%	50%	51%	50%	48%	Dec. 1%
Number reporting	(99)	(99)	(100)	(100)	(100)	

31, 1941, an average of only 30 per cent of all adult patients were under some form of collapse, at the Riverside Hospital only 50 patients out of 342, or 15 per cent, were under that form of treatment; at St. Anthony's Hospital, only 15 per cent likewise; at Bellevue Hospital, where however it must be remembered that patients stay on an average but a short time, the proportion was 24 per

cent, or one out of every 4 patients. In Chicago, in the Tuberculosis Department of the Cook County Hospital, where obviously very sick patients are admitted, only 54 out of 325 patients there, or 16 per cent, were under this type of treatment; at the Missouri State Sanatorium, 25 per cent.

On the other hand, on this same date, namely at the end of 1941, in certain other institutions a comparatively high proportion of all adult patients were under some form of collapse treatment. At the Municipal Sanitarium in Chicago, 640 patients out of a total of 1,112, or 58 per cent; at the Herman Kiefer Hospital in Detroit, 515 out of 793, or 65 per cent; at the Manitoba Sanatorium in Ninette, where many patients are brought in for only a short time for initial induction of pneumothorax, 76 per cent were reported under collapse therapy; at the Michigan State Sanatorium at Howell, "approximately 80 per cent" of all adult patients were reported under collapse; finally, at the American Legion Hospital at Battle Creek, Michigan, 84 per cent.

However, the over-all picture in representative Canadian and American tuberculosis hospitals and sanatoria showed, during the five-year period 1937–1941, that practically half of all adult patients were under some form of collapse therapy and that the trend was towards a slight decline in the proportion so treated.

INDEX OF "PATIENTS" TREATED BY COLLAPSE

In general, the reporting institutions presented their data as the total figure annually of special treatments or surgical procedures to obtain collapse in the treatment of their cases of pulmonary tuberculosis rather than as the number of different patients so treated. Under the circumstances, the problem of comparing the numbers treated by the various institutions necessarily had to be handled by the establishment of a common unit which might be called the "ideal patient," namely, one under continuous treatment for a full year, a unit sometimes called a patient-year. This was particularly necessary when one recalls how variable the average length of stay is in different institutions. The number of patients generally reported as treated annually in hospitals and sanatoria refers too frequently to units not comparable. Thus, for instance, at Bellevue Hospital in New York City—a transfer institution—at the present time the average length of stay of all patients during a given year is close to thirty days only; in other words, a given bed in a year may be used there by 12 different patients. In the upstate New York institutions, the length of stay averages one hundred eighty days; annually, therefore, 2 patients treated per bed. In some of the Veterans' Facilities, patients may be kept for a full year or more. Therefore, in the three places just mentioned patients treated annually might mean, in the first, 12 different individuals; in the second, 2; and, in the third, only one.

As against this variable element in the reported number of patients in the institutions, it was noticed that a far more comparable permanent basis was the average daily census; in the 99 institutions studied, it ranged, among adult patients, only from 30,580 to 32,596 between 1937 and 1941, or by slightly less

than 7 per cent. This is the background here against which the index number of "patients" treated by collapse has been computed.

From reports of a number of representative institutions, which gave both the frequency of procedures and the patients treated, it has been ascertained, first of all, with regard to artificial pneumothorax that throughout a full year there was an average of 32.8 insufflations; in the cases of extrapleural pneumothorax, 40 initial or refills; in pneumoperitoneum, 50 during an entire year; in cases of oleothorax, 11 injections nowadays; that an average of 1.25 pneumonolyses, or of 1.08 phrenic nerve evulsions or crushings, were done per patient; finally, in the case of thoracoplasties, that the average number of stages was 2.41.

Throughout this study, therefore, wherever reference is made to "patients" treated or operated upon, the term is used as referring to an ideal case for a full year, and the ratios established are against the practically steady average daily census of adult patients, rather than in relation to the ordinarily given number of total patients treated in a year by the institutions.

PHRENIC NERVE OPERATION

The first operation reported upon in this survey related to phrenic nerve interruption, its frequency and the trend with regard to its application during the period studied. A total of 18,795 patients were reported by the 99 institutions as having been subjected to phrenic nerve operations. In 1937, phrenic nerve interruption, whether by evulsion or crushing, was reported to have been done on 3,960 occasions; in 1939, a peak was reached with a total of 4,301 such operations; in 1941, in the same institutions, the number was down to 3,895 (table 4, part I).

Most of the phrenic nerve operations were performed, it may be noted, in the Northern midwest institutions where nearly one-third, or 6,546 out of a total of 20,210, were reported for the five-year period. The majority of these operations in the Northern midwest group of institutions were performed in Chicago, at the Municipal Sanitarium; in Detroit, at the Herman Kiefer Hospital or at the Maybury Sanatorium; and, in Wisconsin, at Muirdale. Of all regions, New York City reported the least use of this procedure; 393 instances only.

Following the method of computation and comparison previously stated, it is seen that the number of "patients" subjected to phrenic nerve operations annually during the five-year period 1937–1941, per each 1,000 adult patients on the last day of each year, was 119 (table 4, part II). In the New York City institutions, the index number was only 18 annually. From being 30 there in 1937, it was down to 10 in 1941, a decline of 67 per cent. This particular surgical procedure, as already noted, is being used most often in the Northern midwest group of institutions, the ratio during the five-year period being 219 per 1,000 adult patients seen. Even there, its frequency has been reduced by 24 per cent between 1937 and 1941.

Decreases in the number of "patients" subjected to phrenic nerve interruption were noted in six of the nine regions while, on the other hand, there was some increase in the Mid-Atlantic and Southern section as well as in the Central

inland institutions, where, in a sense, it might be said that the latter were only now catching up with this type of operation done more frequently elsewhere in the past. For all sections, between 1937 and 1941, the trend with regard to

TABLE 4, Part I

Phrenic nerve operations performed during five-year period 1937-1941 at 99 Canadian and American tuberculosis hospitals and sanatoria*

SECTIONS	DURING YEAR					TOTAL
	1937	1938	1939	1940	1941	1937–1941
Canadian (11)	314	398	546	464	474	2,196
New England (6)	308	191	200	238	187	1,124
New York City (10)	122	93	65	67	46	393
Upstate New York (32)	295	191	149	130	117	882
New Jersey (7)	128	99	66	86	48	427
Mid-Atlantic, Southern (9)	246	329	495	551	716	2,337
Central Inland (6)	459	537	630	700	733	3,059
Northern Midwest (11)	1,415	1,617	1,356	1,111	1,047	6,546
Western (7)	673	692	794	560	527	3,246
Total operations	3,960	4,147	4,301	3,907	3,895	20,210
"Patients" subjected	3,682	3,857	3,999	3,633	3,624	18,795

* Evulsion or crushing.

TABLE 4, Part II

Number of "patients" subjected to phrenic nerve operations during five-year period 1937-1941 per each 1,000 patients on December 31 of each year in 99 Canadian and American tuberculosis hospitals and sanatoria*

SECTIONS	DURING YEAR					ANNUALLY	CHANGE
	1937	1938	1939	1940	1941	1937–1941	1941/1937
Canadian (11)	91	109	143	119	121	117	+30 = 33%
New England (6)	133	83	94	113	85	102	−48 = 36%
New York City (10)	30	22	15	15	10	18	−20 = 67%
Upstate New York (32)	73	47	36	32	29	43	−44 = 60%
New Jersey (7)	60	44	28	37	22	38	−38 = 63%
Mid-Atlantic, South'n (9)	51	67	98	105	126	91	+75 = 147%
Central Inland (6)	150	165	184	203	212	184	+62 = 41%
Northern Midwest (11)	234	269	229	185	178	219	−56 = 24%
Western (7)	230	236	271	186	160	215	−70 = 30%
All sections (99)	120	123	126	113	111	119	−9 = 8%

* Adult patients.

phrenic nerve operations was towards a decline of about 8 per cent in the number of "patients" subjected to them.

Observations of representative surgeons, generously and most helpfully submitted in personal communications to the author for the purposes of the present

review, summarize best the prevailing opinion concerning phrenic nerve interruption. They reflect particularly attitudes in different parts of Canada and the United States.

Archibald (Montreal): "Crush now favored. 'Ectomies only for cases in which permanent artificial pneumothorax is expected."
Alexander (Michigan): "We continue to use phrenic operations . . . as we have for a good many years."
Matson (Oregon): "We have . . . given up the exairesis . . . except in selected cases on the right side. We now resort to crushings in from one, two or three places."

ARTIFICIAL PNEUMOTHORAX

Intrapleural pneumothorax is still the method preferred in collapse therapy. In the 99 Canadian and American institutions surveyed, which had, as previously mentioned, a daily patient-census ranging between 30,580 and 32,596 adult patients in 1937 as compared with 1941, it was reported that annually more than one-half million artificial pneumothorax treatments were given to an average number of "patients" treated a full year varying between 16,137 and 17,221[6] (table 5, part I).

In the five-year period under review, reported artificial pneumothorax treatments totalled no less than 2,739,459. Against the total adult census at the end of each year, it is to be noted (table 5, part II) that the index number or ratio of "patients" given pneumothorax treatments reached 533 per each 1,000 adult patients on December 31, 1939, and swung back, at the end of 1941, to 524. Between 1937 and 1941 there was a decline of only one per cent in the ratio of "pneumothorax-patients."

Artificial pneumothorax treatments are given most frequently at the present time in the New Jersey group of hospitals and sanatoria—ratio, 682 "patients" treated per each 1,000 patient-census—and least in the New York City group of institutions—510 per 1,000.

Regionally, five sections studied reported a decrease in the use of pneumothorax during the five-year period 1937–1941; this was greatest in the New York City group where there was a decline of 24 per cent in the number of "patients" treated. Three sections of the United States and the Canadian institutions reported an increase in the number of patients given pneumothorax treatment, the largest, 46 per cent, being in the Mid-Atlantic and Southern group where, however, they are only beginning to follow the practice elsewhere.

It is evident at the present time that, considering all sections surveyed, a

[6] It must be further remembered, since all patients do not necessarily receive the full complement of 33 insufflations a year, that in reality treatments were given to an even greater number of different individuals. As a matter of fact, it is known that, on the basis of taking into account every patient, whether remaining for a long or short stay, altogether in these institutions there have been present about 75,000 different individuals each year. But as already stated, for purposes of exact comparisons at different times and in various parts of the country, the basic unit here is a patient-year. In any case, it is probable that between 25 and 30 per cent of all patients in these institutions were given pneumothorax treatments.

stabilization in the use of artificial pneumothorax treatment seems to have been reached. The impression of surgeons, reflecting their experience and the attitude in their sections, is particularly illuminating.

TABLE 5, Part I

Artificial pneumothorax treatments given during five-year period 1937-1941 at 99 Canadian and American tuberculosis hospitals and sanatoria*

SECTIONS	1937	1938	1939	1940	1941
Canadian (11)	50,245	55,816	59,168	65,238	63,449
New England (6)	41,327	47,613	39,774	32,500	39,811
New York City (10)	75,065	67,623	64,444	66,051	62,933
Upstate New York (32)	69,796	68,680	70,988	64,537	62,706
New Jersey (7)	47,135	47,479	51,958	50,590	46,058
Mid-Atlantic, Southern (9)	52,138	55,109	64,917	78,257	89,083
Central Inland (6)	53,643	56,102	66,463	60,933	58,333
Northern Midwest (11)	87,331	90,131	89,557	88,413	88,333
Western (7)	52,590	49,377	46,776	46,826	54,163
Total treatments	529,270	537,930	554,045	553,345	564,869
Pneumothorax "patients" during year	16,137	16,401	16,891	16,872	17,221
Adult census, Dec. 31	30,580	31,331	31,685	32,248	32,596

* Initial, refills—presumably exclusive of thoracocenteses.
Note: Total treatments during five years, 1937–1941: 2,739,459

TABLE 5, Part II

Number of "patients" given pneumothorax treatments during five-year period 1937-1941 per each 1,000 patients on December 31 of each year in 99 Canadian and American tuberculosis hospitals and sanatoria*

SECTIONS	DURING YEAR					ANNUALLY	CHANGE
	1937	1938	1939	1940	1941	1937–1941	1941/1937
Canadian (11)	475	502	506	546	529	513	+54 = 11%
New England (6)	587	681	611	505	593	597	+6 = 1%
New York City (10)	613	522	492	471	464	510	−149 = 24%
Upstate New York (32)	564	548	563	522	517	543	−47 = 8%
New Jersey (7)	721	693	736	717	682	710	−39 = 5%
Mid-Atlantic, South'n (9)	353	366	420	490	515	432	+162 = 46%
Central Inland (6)	573	566	635	531	510	561	−63 = 11%
Northern Midwest (11)	473	491	495	483	493	487	+20 = 4%
Western (7)	589	551	523	511	540	543	−49 = 8%
All sections (99)	528	523	533	519	524	525	−4 = 1%

* Adult patients.

Archibald (Montreal): "Growing tendency to substitute a thoracoplasty early in all adherent cases of chronic type with good resistance."
Overholt, referring to New England practice, where in 1941 the index ratio was 593 per 1,000, one per cent higher than in 1937, remarks: "We find artificial pneumothorax still

remaining pre-eminently at the top of the temporary forms .... of collapse therapy."
O'Brien, in the Northern midwest secion where between 1937 and 1941 the ratio of patients treated increased from 473 to 493, or by 4 per cent, states that: "The use of artificial pneumothorax .... I think .... has increased."
Matson, from the Western section where the number of patients has come down from 589 to 540, or by 8 per cent, writes: "Artificial pneumothorax is being utilized earlier than it formerly was."
Davidson, of New York City where there has been a 24 per cent decrease in the number of patients given pneumothorax treatments—the ratio of patients formerly 613 per 1,000 being now reduced to 464—remarks pungently: "Artificial pneumothorax is being used less frequently than heretofore by phthisiologists of both ability and conscience. The reason .... is that one cannot lose sight of the fact that in a certain number of cases a

TABLE 6, Part I

Intrapleural pneumonolyses performed during five-year period 1937-1941 at 99 Canadian and American tuberculosis hospitals and sanatoria

SECTIONS	DURING YEAR					TOTAL
	1937	1938	1939	1940	1941	1937–1941
Canadian (11)	206	231	331	482	421	1,671
New England (6)	249	236	255	244	264	1,248
New York City (10)	589	444	472	523	583	2,611
Upstate New York (32)	264	251	217	269	269	1,270
New Jersey (7)	244	334	286	303	304	1,471
Mid-Atlantic, Southern (9)	94	123	207	260	337	1,021
Central Inland (6)	158	179	275	361	409	1,382
Northern Midwest (11)	320	345	436	482	471	2,054
Western (7)	137	76	77	115	156	561
Total operations	2,261	2,219	2,556	3,039	3,214	13,289
"Patients" subjected	1,808	1,775	2,047	2,431	2,571	10,632

very definite pleural complication occurs which in some instances is a blow from which the patient never survives."

INTRAPLEURAL PNEUMONOLYSES

During the five-year period 1937–1941, intrapleural pneumonolyses were reported as having been performed on a total of 13,289 occasions (table 6, part I) on 10,632 "patients." In 1937, the number of these operations was only 2,261 and, in 1941, at the same institutions it had risen to 3,214. In relation to the patient-census, the number of "patients" on whom adhesions were severed averaged annually 67 per each 1,000 adults; in 1937, it was 59; in 1941, it was 79, having risen therefore by 34 per cent (table 6, part II).

The number of pneumonolyses done was larger at most places, except in the New York City group of institutions where artificial pneumothorax treatments are being reduced. Even there, the index number of "patients" treated was still at a high level, 113, at the end of 1941. Strangely, the ratio of pneumonol-

yses was found lowest in the Western group of institutions, practically none being reported at the Fitzsimons General Hospital in Denver.

The surgeons' opinions were as follows:

Overholt, from New England where the ratio changed from 93 to 103, or an increase of 11 per cent, wrote: "We do just as many pneumonolyses as we ever did, but are not tackling the difficult cases."

O'Brien, where in the Northern midwest the ratio has gone up from 45 to 69, an increase of 53 per cent, remarks: "Intrapleural pneumonolyses have increased to a marked degree with an improved technique and instruments."

Matson (Oregon): "Pneumonolysis . . . being utilized more frequently than formerly . . . utilizing the two-puncture method . . . is vastly superior to the one-puncture method."

TABLE 6, Part II

Number of "patients" subjected to intrapleural pneumonolyses during five-year period 1937-1941 per each 1,000 patients on December 31 of each year in 99 Canadian and American tuberculosis hospitals and sanatoria*

SECTIONS	DURING YEAR					ANNUALLY	CHANGE
	1937	1938	1939	1940	1941	1937–1941	1941/1937
Canadian (11)	51	55	74	106	92	77	+41 = 80%
New England (6)	93	89	103	99	103	97	+10 = 11%
New York City (10)	126	90	95	98	113	104	−13 = 10%
Upstate New York (32)	56	53	45	57	58	54	+2 = 4%
New Jersey (7)	98	128	106	113	118	113	+20 = 20%
Mid-Atlantic, South'n (9)	17	21	35	43	51	34	+34 = 200%
Central Inland (6)	44	47	69	90	102	71	+58 = 132%
Northern Midwest (11)	45	49	63	69	69	59	+24 = 53%
Western (7)	40	22	23	33	41	32	+1 = 3%
All sections (99)	59	57	65	75	79	67	+20 = 34%

* Adult patients.

Before closing the subject of pneumonolysis, it should be added that ten institutions reported having performed 202 extrapleural pneumonolyses during the five-year period reviewed.

THORACOPLASTIES

In the 99 Canadian and American tuberculosis hospitals and sanatoria surveyed, the number of thoracoplasty operations performed has been rising steadily (table 7, part I). In 1937, there were 3,950 such operations reported as having been done on 1,639 "patients" and, in 1941, 5,189 on 2,154 "patients." Altogether during this five-year period, 23,435 thoracoplasty operations were performed on 9,725 patients. These figures are to be noted in conjunction with the fact that approximately 250,000 different patients of all types were treated in the institutions studied during the same period. It would seem to indicate that about one out of each 25 patients is now subjected to thoracoplasty or about 4 per cent only of all patients.

More precisely, in relation to the daily census, it was found that the number of "patients" subjected to thoracoplasty per each 1,000 adults had risen from 54 to 66, or by 22 per cent (table 7, part II). The low rate of such operations

TABLE 7, Part I

Thoracoplasties performed during five-year period 1937-1941 at 99 Canadian and American tuberculosis hospitals and sanatoria*

SECTIONS	DURING YEAR					TOTAL
	1937	1938	1939	1940	1941	1937-1941
Canadian (11)	631	712	768	758	678	3,547
New England (6)	289	326	404	493	440	1,952
New York City (10)	463	481	644	723	625	2,936
Upstate New York (32)	393	408	420	459	440	2,120
New Jersey (7)	345	325	423	341	291	1,725
Mid-Atlantic, Southern (9)	175	231	334	325	416	1,481
Central Island (6)	303	404	439	465	452	2,063
Northern Midwest (11)	1,018	1,437	1,173	1,194	1,456	6,278
Western (7)	333	203	164	242	391	1,333
Total operations	3,950	4,527	4,769	5,000	5,189	23,435
"Patients" subjected	1,639	1,878	1,980	2,074	2,154	9,725

* Any stage or revision.

TABLE 7, Part II

Number of "patients" subjected to thoracoplasty during five-year period 1937-1941 per each 1,000 patients on December 31 of each year in 99 Canadian and American tuberculosis hospitals and sanatoria*

SECTIONS	DURING YEAR					ANNUALLY	CHANGE
	1937	1938	1939	1940	1941	1937-1941	1941/1937
Canadian (11)	81	87	90	86	77	84	−4 = 5%
New England (6)	56	63	85	104	89	79	+33 = 59%
New York City (10)	51	51	67	70	63	61	+12 = 24%
Upstate New York (32)	43	44	45	50	49	46	+6 = 14%
New Jersey (7)	72	65	82	66	59	69	−13 = 18%
Mid-Atlantic, South'n (9)	16	21	29	28	33	26	+17 = 106%
Central Inland (6)	40	50	51	55	54	53	+14 = 35%
Northern Midwest (11)	75	106	88	89	111	94	+36 = 48%
Western (7)	51	31	25	36	53	39	+2 = 4%
All sections (99)	54	60	62	64	66	61	+12 = 22%

* Adult patients.

in the Mid-Atlantic or Southern group of institutions, especially in Pennsylvania, was due rather to incomplete reports since their patients up to some time ago were sent from the country sanatoria to the city hospitals for this procedure. However, few cases of thoracoplasty were reported from the Veterans' Facility

at Oteen, North Carolina. But even then in the Mid-Atlantic and Southern group of institutions the rate for patients subjected to thoracoplasty has been increasing materially.

The surgeons' observations, while terse, are revealing of the present attitude and growing appreciation of the favorable results of this still serious operation.

Overholt, where in New England the ratio of patients subjected to thoracoplasty has increased from 56 to 89 per each 1,000 patient-census, or by 59 per cent during the five-year period 1937–1941, writes: "of the various methods of collapse therapy and surgery ... we find ... thoracoplasty leading the permanent forms."

O'Brien, from the Northern midwest where the highest ratio of such operations is now noted, 111 as compared with 75 per 1,000 patient-census in 1937, an increase of 48 per cent, remarks: "The use of thoracoplasty ... has increased almost everywhere. There is a tendency ... to do many more thoracoplasties instead of artificial pneumothorax ...."

Alexander (Michigan): "The tendency is to use thoracoplasty somewhat more often ... because the operative techniques and the preoperative and postoperative management of ... patients have been greatly improved."

TABLE 8

Pneumoperitoneum treatments given during five-year period 1937-1941 at 44 Canadian and American tuberculosis hospitals and sanatoria*

SECTIONS	DURING YEAR					TOTAL
	1937	1938	1939	1940	1941	1937–1941
Canadian (5)	0	0	15	377	3,028	3,405
New England (2)	361	602	1,560	881	723	4,127
New York City (4)	328	141	33	5	16	523
Upstate New York (1)	482	344	16	0	0	842
New Jersey (2)	516	942	100	63	71	1,692
Mid-Atlantic, Southern (7)	1	154	1,714	3,246	3,997	9,112
Central Inland (6)	1,287	1,681	1,405	1,844	2,318	8,535
Northern Midwest (10)	1,371	3,655	3,169	2,311	1,095	11,601
Western (7)	2,865	5,844	3,208	3,609	2,807	18,333
Total treatments	7,211	13,363	11,220	12,336	14,055	58,185
"Patients" treated	179	335	282	307	352	1,455
Adult census, December, 31	19,933	20,426	20,841	21,381	21,889	

* No pneumoperitoneum treatments given at 55 of the 99 institutions surveyed.

PNEUMOPERITONEUM

Only 44 of the 99 hospitals and sanatoria surveyed reported pneumoperitoneum treatments. In five years this procedure seems to have been utilized in less than one per cent of all patients in these particular institutions. Altogether between 1937 and 1941 pneumoperitoneum treatments were given to 1,455 "patients" on 58,185 occasions (table 8). One Canadian institution, the Queen Alexandra Sanatorium of London, Ontario, was trying it in 1941; in the state institutions of North Carolina and Florida, particularly of late, pneumo-

peritoneum treatments were being given; also, at the Missouri State Sanatorium and at Muirdale Sanatorium in Wisconsin; the greatest use was at Olive View Sanatorium of Los Angeles.

Overholt remarks: "Pneumoperitoneum is a procedure . . . too indirect . . . to find much of a place in the treatment of pulmonary tuberculosis."
O'Brien: "Pneumoperitoneums are occasionally used . . . but the popularity they had a few years ago in California has subsided."
Matson: "Pneumoperitoneum definitely has a place, but not the place which was claimed for it three or four years ago. For certain unilateral cases, without bronchial obstruction, where pneumothorax is impossible and the case a poor surgical risk, pneumoperitoneum in combination with a phrenic crush is really a good procedure."

TABLE 9

Oleothorax treatments given during five-year period 1937-1941 at 64 Canadian and American tuberculosis hospitals and sanatoria*

SECTIONS	DURING YEAR					TOTAL
	1937	1938	1939	1940	1941	1937–1941
Canadian (4)	75	33	85	237	180	610
New England (3)	25	59	53	60	43	240
New York City (4)	172	43	48	11	0	274
Upstate New York (30)	737	208	253	165	110	1,473
New Jersey (3)	271	252	227	236	161	1,147
Mid-Atlantic, Southern (5)	11	77	163	267	209	727
Central Inland (3)	228	166	392	447	357	1,590
Northern Midwest (8)	41	68	160	157	205	631
Western (4)	248	156	160	354	343	1,261
Total treatments	1,808	1,062	1,541	1,934	1,608	7,953
"Patients" treated	166	96	142	175	146	725
Adult census, December 31	17,336	17,649	17,642	17,870	17,770	

* No oleothorax treatments given at 25 of the 99 institutions surveyed.

OLEOTHORACES

Oleothorax treatments were not given at 25 of the 99 reporting institutions; among the remaining 64, it was utilized on less than 150 patients in 1941 (table 9). Altogether, during the five-year period 1937–1941, 725 "patients" were given oleothorax treatments on 7,953 occasions. In the 64 institutions reporting oleothoraces the daily census ranged between 17,336 and 17,770 adult patients.

The situation with regard to this particular type of treatment is best summarized by O'Brien, who writes: "Oleothoraces are still used in some parts of the country, but in most communities these too have been abandoned except for isolated patients."

EXTRAPLEURAL PNEUMOTHORAX

Only 27 institutions out of the 99 surveyed reported giving 6,749 extrapleural pneumothorax treatments to 136 patients, practically all of these being done at Olive View Sanatorium in California, especially during the years 1939 and 1940.

The surgeons, when referring to extrapleural pneumothorax treatments, wrote as follows:

Archibald: " . . . this, after the usual vogue, is swinging back to a rather small place . . . . "
Overholt: "We continue to create an extrapleural pneumothorax for certain patients in the 'teen age group . . . this method is extremely limited."
Matson: "As for extrapleural pneumothorax, we prefer the type of operation which I call 'extrapleural pack'."
Alexander: "We use extrapleural pneumothorax and paraffin plombage relatively infrequently."

MONALDI DRAINAGE

Monaldi operations for the drainage of cavities were reported in this group of institutions during the last three years only, namely, from 1939 to 1941. At 30 hospitals or sanatoria a total of 295 such operations were undertaken, most of them at the Sea View Hospital in New York City. The remainder of the Monaldi operations were scattered in the New Jersey group, Northern midwest and Western institutions. In 1939, only 9 such operations were reported; in 1940, 124; in 1941, 162 (table 10, part I).

Selected observations of surgeons on the subject are as follows:

Davidson remarks: "The Monaldi operation, which has taught many of us facts about the pulmonary cavity we never before recognized, at the moment is not being used as a single procedure."
Overholt: "There is a definite place for cavity drainage in the treatment of giant or occluded cavities, but I prefer an open cavernostomy to the Monaldi method."
Matson: "Monaldis seldom effect a cure . . . . "
Alexander: "We use this . . . operation occasionally but are not enthusiastic about it."

LOBECTOMY

Of lobectomies, a scattered few were reported by 25 institutions. Nine such operations were performed in 1937; 14, in 1938; another 16, in 1939; 25, in 1940; and 28, in 1941,—altogether, 92 in five years. The surgeons' views are interesting:

Archibald: "The Los Angeles successes do not appear to have created a 'wave', which I think would be a 'crime wave'."
Matson: "I feel strongly that in . . . cases, where a pneumothorax has been established and there is an atelectatic lung because of a bronchus obstruction and positive sputum, that lobectomies or pneumonectomies will have to be used if we expect to rehabilitate them."
O'Brien: "Lobectomies and pneumonectomies are beginning to have popularity . . . but most thoracic surgeons are still skeptical about their use."
Davidson: "There is unfolding to those of us who are quite interested in the subject the possibilities of treating this chronic disease . . . by excision as evidenced by lobectomy or pneumonectomy."

IN GENERAL, FROM 1937 TO 1941

Briefly, 99 Canadian and American tuberculosis hospitals and sanatoria had an average daily census of adult patients ranging between 30,580 and 32,596

TABLE 10, Part I

Volume of special treatments or surgical procedures during five-year period 1937-1941 at 99 Canadian and American tuberculosis hospitals and sanatoria

TREATMENTS OR OPERATIONS	DURING YEAR					TOTAL
	1937	1938	1939	1940	1941	1937–1941
Phrenic nerve (99)	3,960	4,147	4,301	3,907	3,895	20,210
Artificial pneumothorax (99)	529,270	537,930	554,045	553,345	564,869	2,739,459
Extrapleural pneumothorax (27)	21	818	2,792	2,383	735	6,749
Intrapleural pneumonolysis (99)	2,261	2,219	2,556	3,039	3,214	13,289
Extrapleural pneumonolysis (10)	32	45	57	47	21	202
Thoracoplasty (99)	3,950	4,527	4,769	5,000	5,189	23,435
Pneumoperitoneum (44)	7,211	13,363	11,220	12,336	14,055	58,185
Oleothorax (64)	1,808	1,062	1,541	1,934	1,608	7,953
"Monaldi" (30)	0	0	9	124	162	295
Lobectomy (25)	9	14	16	25	28	92
Total hospital or sanatorium patients*	74,295	74,132	73,961	75,738	77,588	249,870

Note: Inset numbers refer to institutions reporting particular procedures.

* The figure of the total individual patients treated annually in the hospitals and sanatoria is based on the sum of all patients discharged, alive or dead, children or adults, during the year plus the adult census, namely, those remaining, on December 31 of each year. The latter lacks, however, the comparatively small number of children in these institutions on that day. According to the findings in the survey of the American Medical Association in 1938, the patient-census for the entire country, in this series of services which exclude preventoria, showed an average of 8 per cent of them being children. This proportion added to the census of adult patients, in the 99 Canadian and American hospitals and sanatoria, would increase, in 1937, the total patients treated by 2,659; in 1938, by 2,724; in 1939, by 2,755; in 1940, by 2,804; and in 1941, by 2,834. And accordingly the total for all patients treated during the five-year period, when, in this case, only the last census needs correction, would be raised by 2,834 to 252,704.

But against this addition of the children in the last day's census to the number treated, there must be borne in mind that the figure of total patients discharged included patients readmitted and redischarged so that in reality the strictly different and larger number of individuals just mentioned needs to be discounted. The same survey of the American Medical Association, while acknowledging lack of data on the exact number of readmissions, contained however the significant statement that, for the entire country when admissions numbered 122,342, therein were "7,254 patients received by transfer from other institutions," a group equal to 6 per cent of the total number. While this recognizes transfers from other institutions, it ignores patients readmitted to the same institution.

The net effect of adding to the patient-census to provide for children patients, and of discounting the total discharged for the inclusion therein of readmissions and transfers, is probably small. All this leads to the conclusion that the figures given in table 10 of approximately 75,000 patients treated annually in the 99 institutions surveyed is very close to the exact number of different individuals seen. The value of this basic figure of 75,000 or so patients treated annually is that it enables one to establish the proportion of all patients, besides the ratio to the daily census, under some particular form of collapse therapy.

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during the five-year period 1937–1941. Annually they treated—under the ordinary methods of bed rest, hygienic-dietetic regimen, collapse or surgery—from 74,295 to 77,588 patients; in five years, a total of 249,870. On December 31 of each of the years just mentioned, they reported having had from 14,922 to 15,791 adult patients under some form of collapse therapy, which was finally 48 per cent of their total adult patient-census—a decrease of only one per cent from what the proportion was at the end of 1937.

During the five-year period 1937–1941, the total treatments given or operations performed numbered as follows: phrenic nerve interruptions, 20,210; artificial

TABLE 10, Part II

"Patients" given special treatments or subjected to operations during five-year period 1937-1941 at 99 Canadian and American tuberculosis hospitals and sanatoria*

FORM OF TREATMENT TYPE OF OPERATION	ENTIRE YEAR					TOTAL
	1937	1938	1939	1940	1941	1937–1941
Phrenic nerve (99)	3,682	3,857	3,999	3,633	3,624	18,795
Artificial pneumothorax (99)	16,137	16,401	16,891	16,872	17,221	83,522
Extrapleural pneumothorax (27)	1	16	56	48	15	136
Intrapleural pneumonolysis (99)	1,808	1,775	2,047	2,431	2,571	10,632
Extrapleural pneumonolysis (10)	32	45	57	47	21	202
Thoracoplasty (99)	1,639	1,878	1,980	2,074	2,154	9,725
Pneumoperitoneum (44)	179	335	282	307	352	1,455
Oleothorax (64)	166	96	142	175	146	725
"Monaldi" (30)	0	0	9	124	162	295
Lobectomy (25)	9	14	16	25	28	92
Adult census (99) December 31	30,580	31,331	31,685	32,248	32,596	

* Term "patient" refers to ideal case treated a full year: Pneumothorax, averaging 32.8 insufflations per year; extrapleural pneumothorax, 50; pneumoperitoneum, 40; oleothorax, 11; intrapleural pneumonolysis, 1.25 each patient; phrenic, 1.08 evulsions or crushings; thoracoplasty, 2.41 stages or revisions; remaining operations, 1 per patient.

Note: Inset number refers to institutions reporting particular procedures.

pneumothoraces, 2,739,459; extrapleural pneumothoraces, 6,749; intrapleural pneumonolyses, 13,289; extrapleural pneumonolyses, 202; thoracoplasties, 23,435; pneumoperitoneums, 58,185; oleothoraces, 7,953; "Monaldis", 295; and lobectomies, 92 (table 10, part I).

"Patients"[7] treated or subjected to operation, among the total of 249,870 different individuals in these institutions, anytime between January 1, 1937 and December 31, 1941, numbered as follows: 83,522 given artificial pneumothorax treatments; 18,795, phrenic nerve interruptions; 10,834, intra- or extrapleural pneumonolyses; 9,725 had various stages of thoracoplasty performed; 1,455, pneumoperitoneum treatments; 725 oleothoraces; 295, Monaldi operations; 92 lobectomies (table 10, part II).

[7] Ideal cases as previously defined.

With regard to the trend as to the type of procedures, as revealed by variations between 1937 and 1941, in the index number of "patients" treated or subjected to operation per each 1,000 adult patient-census, it was found that those given artificial pneumothorax, and which numbered 528 at first, were down to 524 in 1941, a change of 4 points only or of one per cent. As against 120 per 1,000 patient-census who had phrenic nerve interruptions in 1937, the number was down to 111 in 1941, a decrease of 8 per cent.

Intrapleural pneumonolyses, previously done on 59 per 1,000 census had risen to 79 by the end of 1941, or by 34 per cent. Whereas 54 had thoracoplasties in 1937, their number was 66 per 1,000 census in 1941, an increase of 12, or of 22 per cent. "Patients" given pneumoperitoneum treatments were slightly more

TABLE 10, Part III

Number of "patients" given special treatments or subjected to operations during five-year period 1937-1941 per each 1,000 patients† on December 31 of each year at 99 Canadian and American tuberculosis hospitals and sanatoria*

TREATMENT OR OPERATION	DURING YEAR					ANNUALLY	CHANGE
	1937	1938	1939	1940	1941	1937–1941	1941/1937
Phrenic nerve (99)	120	123	126	113	111	119	−9 = 8%
Artificial pneumothorax (99)	528	523	533	519	524	525	−4 = 1%
Extrapleural pneumothorax (27)	...	0.6	1.9	1.7	0.5	0.9	+nominal
Intrapleural pneumonolysis (99)	59	57	65	75	79	67	+20 = 34%
Extrapleural pneumonolysis (10)	1.2	1.6	2.0	1.6	0.7	1.4	?nominal
Thoracoplasty (99)	54	60	62	64	66	61	+12 = 22%
Pneumoperitoneum (44)	7	12	10	11	12	10	+5 = 71%
Oleothorax (64)	5.4	3.1	4.5	5.4	4.5	4.6	−0.9 = 17%
"Monaldi" (30)	0	0	0.3	4.3	5.5	2.1	+nominal
Lobectomy (25)	0.3	0.5	0.6	0.9	0.9	0.7	+nominal

* Patients treated entire year.
† Adult patients.

numerous, 12 per 1,000 as against 7, but the change was not significant. "Patients" who had oleothoraces—never numerous—markedly declined further in number by 17 per cent. Monaldi operations were having some vogue between 1939 and 1941.

Overholt characterized well the situation at this time when he wrote that "collapse therapy picture in pulmonary tuberculosis . . . a changing one . . . a sifting out process going on . . . agreement rather widespread on fundamental points."

SEVEN YEARS BACK—1941 VERSUS 1934

Passing from the record during the five-year period 1937–1941, another interesting and slightly older landmark against which the situation in 1941

may be viewed is to be had from the limited, but probably very significant, data referring to pneumothorax and certain surgical procedures in the treatment of pulmonary tuberculosis as reported in the survey (1) of the American Medical Association for the year 1934 (table 11).

TABLE 11

Frequency of collapse therapy procedures in tuberculosis hospitals and sanatoria in 1934 and 1941

	YEAR	
	1934	1941
Institutions reporting	502*	99†
Adult patient census, given day	70,354‡	32,596¶
Artificial pneumothorax:		
Number of treatments	433,890	564,869
"Patients" treated	13,228	17,221
"Patients," per 1,000 census§	188	524
Phrenic nerve interruption:		
Number of operations	7,695	3,895
"Patients" subjected	7,125	3,624
"Patients," per 1,000 census§	101	111
Thoracoplasty:		
Number of operations	2,935	5,189
"Patients" subjected	1,218	2,154
"Patients," per 1,000 census§	17	66
Pneumonolysis:		
Number of operations	929	3,214
"Patients" subjected	743	2,571
"Patients," per 1,000 census§	11	79
Oleothorax:		
Number of treatments	2,076	1,608
"Patients" treated	189	146
"Patients," per 1,000 census§	2.6	4.5

* 401 sanatoria and 101 tuberculosis hospital services in the United States; survey, American Medical Association (1).

† 11 Canadian and 88 American institutions.

‡ On "day reporting."

§ "Patients" treated, or subjected to operation, during year, per each 1,000 adult patient census on given day.

¶ December 31, 1941.

Note: Term "patient," as previously defined, refers to ideal case treated a full year (see footnote, table 10, part II). Ratios of index numbers of "patients" treated or operated upon in 1941 compared with 1934 were as follows: pneumothorax, 2.8:1; phrenic interruption, 1.1:1; thoracoplasty, 3.9:1; pneumonolysis, 7.2:1; and, oleothorax, 1.7:1.

Further back too, we have Leslie and Anderson's statements (2) that from Whitney's survey for the National Tuberculosis Association of civilian sanatoria in 1931 "little more than 10 per cent of all sanatorium patients throughout the country were receiving collapse therapy in that year." Also, by the same writers, that in 1933 the Committee on Treatment of the American Sanatorium

Association, when surveying 112 institutions, gathered reports which "indicated that 39 per cent" of the patients "received some form of collapse therapy." Leslie and Anderson added, however, about the latter that these places undoubtedly included "the majority of institutions most advanced in collapse therapy" where might be presented "a higher average . . . than was actually being done throughout the whole country in 1933."

The survey, for 1934, by the Council on Medical Education and Hospitals of the American Medical Association dealt with no less than 502 institutions throughout the country and covered 70,534 adult patients, or a little over twice the number included in the present study, and yet, except in the case of phrenic nerve interruptions or oleothoraces, the number of treatments or operations to obtain collapse were fewer.

For instance—as against, in 1941, 564,869 artificial pneumothorax treatments given to 17,221 patients in 99 institutions with an adult patient-census of 32,596—there were given, in 1934, in the 502 reporting sanatoria or tuberculosis hospital services, 433,890 treatments to 13,228 "patients." In terms of those treated per 1,000 adult patient-census, in 1934 there were only 188 pneumothorax "patients" compared with 524 in 1941. In other words, for each one patient given artificial pneumothorax in 1934 there are on an average 2.8 or so treated nowadays.

But as against 111 who now have phrenic nerve interruptions, already in 1934 101 were likewise subjected to this operation—a ratio therefore of 1.1 recently as against one previously.

For thoracoplasties, as against 66 "patients" per 1,000 census operated upon in 1941, in 1934 there were only 17; in other words, practically four times as many patients are now operated upon in this manner (3.9:1).

The severing of adhesions is likewise being performed much more frequently. In 1941, 79 "patients" per 1,000 census as against 11 formerly, or a ratio of 7.2:1.

Oleothoraces are apparently still holding their own, but with only 4.5 "patients" per 1,000 in 1941 as against 2.6 in 1934, a ratio of 1.7:1.

This broad, representative survey of the American Medical Association, for the year 1934 would indicate that at that time approximately 14,280 patients were under some form of collapse therapy on a given day out of the daily adult census of 70,354, or 20 per cent.

From the several authorities just mentioned it may, therefore, be observed that on an average for the United States as a whole, in 1931, 10 per cent of all patients in specialized institutions for the treatment of tuberculosis, or in hospital services for the reception of that type of patient, were under some form of collapse therapy as commonly practiced; in 1933, in a selected, limited, group of sanatoria, 39 per cent; in 1934, considering a nation-wide series of sanatoria and tuberculosis hospital departments, 20 per cent; in 1937, 49 per cent; in 1939, 51 per cent; and, in 1941, 48 per cent.

TABLE 12

Canada and United States—One hundred and one tuberculosis hospitals and sanatoria—Mortality ratio of patients discharged† during five-year period 1937-1941*

SECTIONS	1937	1938	1939	1940	1941	FIVE YEARS 1937–1941
Canadian (11):						
Total discharged	3,465	3,366	3,387	3,579	3,762	17,559
Died in institutions	569	509	528	521	584	2,711
Mortality ratio	16%	15%	16%	15%	16%	15%
New England (6):						
Total discharged	1,740	1,881	1,836	1,899	1,993	9,349
Died in institutions	402	478	442	508	520	2,350
Mortality ratio	23%	25%	24%	27%	26%	25%
New York City (10):						
Total discharged	8,753	8,354	7,951	8,369	8,644	42,071
Died in institutions	1,806	1,614	1,626	1,622	1,675	8,343
Mortality ratio	21%	19%	20%	19%	19%	20%
Upstate New York (32):						
Total discharged	5,245	4,611	4,389	4,438	4,253	22,936
Died in institutions	1,064	992	994	1,099	961	5,110
Mortality ratio	20%	22%	23%	25%	23%	22%
New Jersey (7):						
Total discharged	2,533	2,537	2,606	2,710	2,678	13,064
Died in institutions	680	690	643	745	697	3,455
Mortality ratio	27%	27%	25%	27%	26%	26%
Mid-Atlantic, Southern (9):						
Total discharged	6,249	5,524	5,812	5,828	6,211	29,624
Died in institutions	979	871	1,009	1,079	1,208	5,146
Mortality ratio	16%	16%	17%	19%	19%	17%
Central Inland (7):						
Total discharged	5,227	5,632	5,728	5,856	6,076	28,519
Died in institutions	745	773	740	857	937	4,052
Mortality ratio	14%	14%	13%	15%	15%	14%
Northern Midwest (11):						
Total discharged	5,418	5,352	6,392	6,306	6,424	29,892
Died in institutions	1,135	1,072	1,757	1,753	1,709	7,426
Mortality ratio	21%	20%	27%	28%	27%	25%
Western (8):						
Total discharged	4,662	4,638	5,064	5,416	5,929	25,709
Died in institutions	633	619	657	730	693	3,332
Mortality ratio	14%	13%	13%	13%	12%	13%
All sections (101):						
Total discharged	43,292	41,895	43,165	44,401	45,970	218,723
Died in institutions	8,013	7,618	8,396	8,914	8,984	41,925
Mortality ratio	19%	18%	19%	20%	20%	19%

* Beds represented in 1938, 33,450.

† Discharged alive or dead.

Part II

General Mortality Ratio[8] of In-Patients of Tuberculosis Hospitals and Sanatoria

While it would have been desirable to obtain mortality figures which might have given specific indications of the results of collapse therapy, it was not possible to do so in this summary survey for obvious reasons: first, that the institutions had knowledge generally of only the immediate mortality within their confines and yet it is the ultimate results that are decisive in a chronic disease like tuberculosis; second, the information to be worthwhile would have had to be subdivided for length of stay and for the types of patients as well as for form of treatment or operation; finally, there would remain the need, in interpreting the findings, of truly comparable controls always so difficult to define and to obtain.

But the Canadian and American institutions surveyed did make available reports of all the deaths of their patients which occurred there during the period

TABLE 13

*England—Pulmonary tuberculosis "patients in approved residential institutions"—Mortality ratio during five-year period 1934–1938**

YEARS	1934	1935	1936	1937	1938	FIVE YEARS 1934–1938
Total discharged†.....	37,505	38,122	39,435	39,440	39,791	194,293
Died in institutions.....	6,647	7,020	7,428	8,024	7,834	36,953
Mortality ratio.....	18%	18%	19%	20%	20%	19%

* From Annual Reports, Ministry of Health.
† Discharged alive or dead.

under review. And since so large a proportion of all their patients, namely half, were under some form of collapse therapy during the period 1937–1941, it was deemed of interest to assemble the general mortality figures of in-patients and to study their trend; likewise, to obtain some comparable figures abroad as well as data previous to 1931 when treatment of pulmonary tuberculosis by collapse was hardly in use.

TYPE OF CASES IN HOSPITALS

There is available a certain amount of information indicative, at least in the over-all picture, of the type of cases admitted to tuberculosis sanatoria or hospitals. The results of several representative surveys are worth studying (table 14). It should be noted that three of them were made in years included in the period 1937–1941: two refer to the large group of institutions which are

[8] The majority of patients in tuberculosis institutions, when first admitted, are found to be in either moderately or far advanced stages of the disease. Practically all the deaths in these hospitals or sanatoria are due to tuberculosis.

members of the Sanatorium Conference of Metropolitan New York; the third was made by the American Medical Association.

The first nation-wide survey on tuberculosis hospitalization in the United States made by the author disclosed that in 1925, among 34,686 patients admitted to 176 institutions, 16 per cent only of the patients were, on admission, in the minimal stage and 50 per cent already far advanced. In the survey for the year 1931 by Whitney, the proportion of far advanced cases was 54 per cent; the surveys of the American Medical Association, in 1934 and 1938, disclosed practically the same situation, 57 per cent and 55 per cent, respectively, in the third stage. In 1937 and in 1941, the writer found among patients admitted to institutions of the New York Metropolitan Area, in the first instance, 57 per cent of far advanced cases and, in 1941, 53 per cent.

In the main, therefore, it should be said that for some general, broad, underlying condition whenever dealing with pulmonary tuberculosis, the type of case coming up for treatment in institutions has remained to date fairly similar. As

TABLE 14

Condition of cases of pulmonary tuberculosis on admission to tuberculosis hospitals and sanatoria, 1925 to 1941

YEARS	1925	1931	1934	1937	1938	1941
Area surveyed	United States	United States	United States	New York, New Jersey	United States	New York New Jersey
Author	Drolet (3)	Whitney (4)	A. M. A. (1)	Drolet (5)	A. M. A. (6)	Drolet (7)
Institutions	176	274	494	43	872	48
Patients	34,686	36,665	66,861	14,392	80,088	14,291
Minimal stage	16%	16%	13%	10%	13%	13%
Far advanced	50%	54%	57%	57%	55%	53%

a matter of fact, when one realizes the ever widening use of the X-ray for the examination of the chest nowadays and its revelations, it is probable that the proportion of patients said to have been far advanced in the past was actually greater than stated. In the main, however, the possible results of treatment during the recent five-year period 1937–1941, as far as they were dependent upon the type of cases admitted, were not subject to much modification. There was present, if anything, a slightly more favorable opportunity. As previously noted, up to 1933 or 1934 collapse therapy had not yet reached its maximum use, but between 1937 and 1941, for the country as a whole, practically half of all patients in these institutions had the benefit of these special treatments or surgical procedures; in some institutions they were applied to even as high a proportion as 80 per cent of all the patients. Collapse therapy in some form or other has, therefore, had a fairly extensive trial!

DEATHS IN HOSPITALS AND SANATORIA

Between 1937 and 1941, from 101 large institutions of Canada and the United States 218,723 patients were discharged, either alive or through death (table

12). The number of deaths at these places during that same period totalled 41,925, a mortality ratio of 19 per cent; this proportion varied little through the five years, being 19 per cent in 1937 and respectively 18 per cent, 19 per cent, 20 per cent and 20 per cent in the succeeding four years; annually, therefore, no significant differences.

In different sections of the country, however—obviously depending upon the type of cases at certain places, or even perhaps due to varying length of stay or treatment—there were noticeable differences in mortality rates, difficult to explain or to interpret with the limited information at hand. It is to be noted also that in Canada, where in general low tuberculosis rates prevail among the population, mostly Anglo-Saxon, during the five-year period the mortality ratio averaged 15 per cent. It was similarly low, in fact slightly less, among the patients of the Western group of American institutions where the death rate averaged 13 per cent; also, in the Central inland group[9] where it was 14 per cent. Higher mortality ratios, 25 and 26 per cent, were steadily recorded in the New England group and in the New Jersey series of institutions studied. The hospitals with the largest number of patients, namely those in New York City, where 42,071 patients were discharged during the period 1937–1941, recorded a mortality ratio averaging 20 per cent. But, as noted, the general overall picture during the five years studied showed no improvement in the number of deaths. There must be acknowledged, above all, in the development and progress of pulmonary tuberculosis a certain natural evolution.

INSTITUTIONAL MORTALITY IN ENGLAND

This constancy in the death rate of patients in institutions would seem to be borne out by available similar information, for instance, in England for the entire five years prior to World War II, namely, from 1934 to 1938. Records at hand (table 13) cover 194,293 patients, almost as many as those observed in the present American survey. In the English group of institutions, it will be noted that there were 36,953 deaths, or a mortality ratio of 19 per cent, identically the same as the average for the Canadian and American series. Furthermore, in England, the death rate, if anything, from 1934 to 1938 has been rising slightly from 18 per cent to 20 per cent, but it is tending to oscillate towards the identical proportion observed here.

Without desiring to appraise precisely and only the influence of collapse measures on the results of treatment or the mortality of patients in institutions, still in view of the fact of the greater use recently, or rather addition of these procedures to the simpler or older form of sanatorium regimen, it is worthwhile, and in fact very important, to study available records of institutional mortality at different periods of time. The surveys of the American Medical Association (table 15) show, for instance, in 1934, when only 20 per cent of patients were treated by collapse, a general mortality ratio of 17 per cent; in 1938, the ratio was 19 per cent, when we know that this special form of treatment was then being utilized that year in 50 per cent of all adult patients.

[9] For institutions included therein see list at end of article.

A survey by the writer of the situation in the Metropolitan New York Area during the ten-year period 1927–1936 disclosed here a mortality ratio of 21 per cent (8). Another, in 1925, this time extending to institutions throughout the United States, revealed the sanatorium or hospital mortality ratio for tuberculosis patients to be 20 per cent (3).

But more striking and little appreciated at first as to its broad significance was a casual statement only recently noted in the report of Whitney (4) in her survey of tuberculosis hospitalization in the United States. She had taken care to secure from the institutions reporting the figures *of all admissions since their first opening*, with proper qualification as to the number of readmissions and, finally, of all the deaths which occurred in these institutions during that time. As a result, she ascertained that up to July 1, 1931, American sanatoria and tuberculosis hospital departments, since their opening had admitted no less than 1,371,200 patients of which 36,954 were readmissions and that altogether during

TABLE 15

Mortality ratio of patients in tuberculosis hospitals and sanatoria at different times up to 1941—United States, Canada, England

Area	United States	United States	New York, New Jersey	United States, Am. Med. Ass'n.		England	U. S. & Canada
Institutions	184 (a)	"all" (b)	28–40 (c)	544 (d)	571 (e)	534 (f)	101
Years	1925	–1931	1927–1936	1934	1938	1934–1938	1937–1941
Total discharged*	38,288	1,277,400	156,748	95,925	117,062	194,293	218,723
Died in institutions	7,705	246,600	32,495	16,229	22,081	36,953	41,925
Mortality ratio	20%	19%	21%	17%	19%	19%	19%

* Discharged alive or dead, except in the 1931 survey which refers to all "new" admissions since the opening of American sanatoria or tuberculosis hospitals up to July 1, 1931.

Authors: (a) Drolet (3), Tuberculosis Hospitalization; (b) Whitney (4), Tuberculosis Hospitalization; (c) Drolet (8), Case Fatality Rates in Tuberculosis; (d) (e) American Medical Association (1) (6), Survey of Tuberculosis Hospitals and Sanatoriums; (f) From Annual Reports, Ministry of Health.

that period there had been 246,600 deaths, indicating, she carefully noted, that "19 per cent of patients admitted are discharged by death." In other words, we have here on the broadest basis possible that the general mortality ratio of in-patients in American institutions up to the year 1931—pre-collapse therapy days—was exactly at the same level which has again been recorded for the period 1937–1941. And a similar situation is now reported for the group of all the "approved residential institutions" in England from 1934 to 1938.

Pulmonary tuberculosis, viewed broadly—either from the type of cases admitted for treatment in institutions or from the mortality ratio of those under twenty-four hour observation or care therein—still seems to pursue at the present time an unchanged, unmodified, natural course of its own.

DISCUSSION ON VALUE OF "SANATORIUM TREATMENT"

Because *under present conditions* the mortality ratio of patients in tuberculosis hospitals or sanatoria remains constant at the apparent level of one death out

of every 5 patients hospitalized, it would be unwarranted and unfair to conclude that so-called "sanatorium treatment" or collapse therapy has been a failure. First, it is merely necessary to recall that tuberculosis case fatality in the general community (8) remains at between 40 and 50 per cent to see at once an immense value in institutional treatment. True many of the patients who finally die at home and, therefore, are charged against the community mortality ratio have previously been in institutions, but not necessarily all of them; in fact, a material number of tuberculosis cases, in some places running from 10 to 20 per cent of all tuberculosis deaths, are still being first registered only through death records or very shortly previous to death.

Second, collapse therapy, especially its most effective procedure, thoracoplasty, undoubtedly achieves results with far advanced cases of tuberculosis that were never attained before—but this is, or can be, done with barely more than 4 or 5 per cent of institutionalized cases. The weakest collapse measure is probably artificial pneumothorax. To begin with, it requires, for its best application, cases relatively free of adhesions and, therefore, is selective; finally, in too many pneumothorax cases, the majority, fluid—a complication—develops.

One important gain from collapse therapy, particularly advantageous from a public health point of view, is the number of conversions to negative of positive-sputum cases. But collapse measures cannot be expected to replace tissues where disease has been so advanced as to cause excavation. It would be as fair to deny the value of surgery in cancer, because the knife cannot save where malignancy has spread beyond reach. Also, it must be stated that, in certain cases, collapse therapy enables patients, without entering institutions, to continue their gainful occupation while being under treatment.

Sanatorium treatment undoubtedly, even when patients ultimately die of tuberculosis, has lengthened the lives of many and enabled them to continue performing worthwhile tasks longer than they would have been able to do otherwise.

Another apparently indirect, but very real and extensive, service rendered by the sanatoria and tuberculosis hospitals has been the practical health education and training in hygienic living which a stay in these institutions gives to their patients. When one recalls that, since the opening of tuberculosis institutions in the United States up to the present time, more than two million patients have been admitted there, we can better realize the far-reaching influence upon this large group, and through them to their families as well, that has been exerted by the daily witnessing and practicing of hygienic measures. Cleanliness, constant ventilation, are so readily accepted now as necessities for healthy living that one is apt to forget how but a generation ago the importance of fresh air was not appreciated and there was a real dread of night air, or how little thought was given to disposal of infectious sputum. The tuberculosis institutions have taught thousands upon thousands all this most effectively.

Sanatorium or tuberculosis hospital treatment, frankly, has had so far comparatively little opportunity to show its possibilities. It will reveal its full value, first, when the majority of patients admitted for treatment are in the

early stage of the disease instead of, as now, being far advanced or terminal;[10] second, when conditions interfering with adequate duration of treatment are corrected—hospital crowding, poor food, unhygienic arrangements, unattractive surroundings, social and economic worries; third, when there will be intelligent, experienced selection of cases for special treatment and surgical attention, with modern facilities[11] available, not only at a few places but at least in every institution supported or subsidized by public funds. Then, and not until then, will it be truly said that "tuberculosis is curable" and in the community, if equally wise, "preventable"!

SUMMARY

1. Reports on the extent of collapse procedures in the treatment of pulmonary tuberculosis, during the five-year period 1937–1941, have been obtained from 100 or so large-sized hospitals and sanatoria, with a total bed capacity of nearly one-third of the entire tuberculosis facilities in the United States and Canada.

2. On December 31, 1937, in 99 Canadian and American tuberculosis hospitals and sanatoria, when the census of adult patients totalled 30,580, 14,922 of them were reported to be under some form of collapse therapy—a proportion of 49 per cent. At the end of 1941, the ratio was practically unchanged, being 48 per cent.

3. On December 31, 1941, in the institutions surveyed, the proportion of adult patients under any form of collapse therapy, as compared with that of five years previously, had increased in three sections of North America and decreased in six. The ratio was highest in the Western group of institutions, 58 per cent; lowest, in the New York City group, 30 per cent.

4. Patients subjected to phrenic nerve operations averaged 120 per each 1,000 adult patients on December 31, 1937, and 111 on the same date in 1941, a decline of 8 per cent. This procedure was used most frequently in the Northern midwest group of institutions; ratio 219, annually; and, least in the New York City hospitals, ratio, 18.

5. Patients given artificial pneumothorax treatments averaged 528 per each 1,000 adult patients on December 31, 1937, and 524 on the same date in 1941, a change of only 1 per cent. No less than 2,739,459 pneumothorax treatments were reported for the five years 1937 to 1941. A decline of 24 per cent in the use of pneumothorax was reported by the New York City group of institutions. This form of treatment is now most common in the New Jersey hospitals and sanatoria.

6. Intrapleural pneumonolyses are now increasingly done, the ratio of patients so subjected having risen from 59 in 1937 to 79 in 1941, or by 34 per cent.

7. Thoracoplasties, in the institutions surveyed, have increased in number from 3,950 in 1937 to 5,189 in 1941, the ratio having risen by 22 per cent in five

[10] Twenty-five to 30 per cent of the deaths in institutions now occur within thirty days of admission.

[11] In many sanatoria an insufficiency of "infirmary" facilities limits unduly the number of patients who may be given complete bed-rest.

years. On an average, it has been applied to only 4 per cent of all patients. This operation is performed most frequently in the Northern midwest institutions.

8. Pneumoperitoneum and oleothorax treatments were given to relatively few patients; annually, during the period 1937–1941, of the first only 10, and, of the second, 5 per each 1,000 adult patient-census on a given day.

9. The Monaldi type of operation was reported as having been done on only 295 occasions; lobectomies, on 92.

10. In 1934, an average of 20 per cent of the adult patients in American institutions were undergoing some form of collapse for the treatment of pulmonary tuberculosis; this proportion reached a peak of 51 per cent in 1939, and receded to 48 per cent in 1941.

11. The mortality ratio of patients while in institutions averaged 19 per cent of all discharges during the five-year period 1937–1941, remaining practically constant; it was lowest, 13 per cent, in the Western group, and highest, 26, in the New Jersey section. In England, during the five years 1934 to 1938, in "approved residential institutions" which treated an equally large number of patients, the mortality ratio was identical, 19 per cent.

12. Even now, more than half of all the cases of pulmonary tuberculosis entering American institutions are already in the far advanced stage of the disease when first admitted; the proportion has remained similar, namely, between 50 and 57 per cent since 1925 when the first nation-wide survey was made.

13. The mortality ratio of patients in tuberculosis hospitals and sanatoria—considering the general "over-all" picture—has remained the same since collapse therapy came into wide use to what it was in the United States during the entire period prior to 1931. The natural evolution of pulmonary tuberculosis continues unmodified.

14. The greatest value of tuberculosis hospitals and sanatoria lies in the segregation of infectious cases and in the prevention of the spread of infection in the community. Sanatorium treatment has not had a fair opportunity: too many of the patients admitted are in the last stage of the disease; too many leave against advice after an inadequate stay. In isolated, selected instances certain surgical operations achieve remarkable results and save a few lives; too often, other collapse therapy measures unfortunately add complications to already serious cases; after-care is a meaningless term at present to the majority of the discharged patients who too frequently must return to unfavorable living and working conditions.

SUMARIO

1. De unos 100 grandes hospitales y sanatorios, con una capacidad total de casi la tercera parte de todas las camas disponibles para tuberculosos en los Estados Unidos y el Canadá, se han obtenido informes relativos a la aplicación de la colapsoterapia en la tuberculosis pulmonar durante el quinquenio 1937–1941.

2. De acuerdo con estos datos, el 31 de diciembre de 1941, en 99 hospitales y sanatorios para tuberculosos del Canadá y Estados Unidos, en los que el número

de enfermos adultos representaba 30,580, 14,922 (49 por ciento), se encontraban bajo alguna forma de colapsoterapia. A fines de 1941 la proporción era casi idéntica: 48 por ciento.

3. El 3 de diciembre de 1941 en las instituciones estudiadas la proporción de enfermos adultos que recibían alguna forma de colapsoterapia, comparada con la de cinco años antes, había aumentado en tres regiones de Norte América y disminuído en seis. La proporción mayor correspondió al grupo de las instituciones del Oeste: 58 por ciento, y la menor al de la ciudad de Nueva York: 30 por ciento.

4. Los enfermos sometidos a operaciones en el nervio frénico promediaban 120 por 1,000 enfermos adultos el 31 de diciembre de 1937, y 111 en la fecha correspondiente de 1941, o sea una baja de 8 por ciento. Este procedimiento fué utilizado más frecuentemente en el grupo de instituciones de la porción septentrional del Meso-Oeste: proporción anual, 219; y menos de todo en los hospitales de la ciudad de Nueva York.

5. Los enfermos que recibían el neumotórax terapéutico promediaban 528 por cada 1,000 enfermos adultos el 31 de diciembre de 1937, y 524 en la misma fecha de 1941, o sea un cambio apenas de 1 por ciento. No menos de 2,739,459 tratamientos de neumotórax fueron comunicados para el quinquenio 1937–1941. En el grupo de instituciones de la ciudad de Nueva York se comunicó una baja de 24 por ciento en el empleo del neumotórax. Este tratamiento alcanza hoy día su frecuencia mayor en los hospitales y sanatorios del Estado de Nueva Jersey.

6. Va en aumento constante la ejecución de la neumolisis intrapleural, habiéndose elevado la proporción de los enfermos así tratados de 59 en 1937 a 79 en 1941, o sea 34 por ciento.

7. En las instituciones estudiadas, las toracoplastias han aumentado de 3,950 en 1937 a 5,189 en 1941, o sea un aumento de 22 por ciento en cinco años. En conjunto, esta técnica sólo ha sido aplicada a 4 por ciento de todos los enfermos. La operación se ejecutó con mayor frecuencia en las instituciones de la parte septentrional del Meso-oeste.

8. Relativamente pocos enfermos han recibido como tratamiento el neumoperitoneo y el oleotórax; anualmente, durante el quinquenio 1937–1941, solamente 10 de los primeros y 5 de los segundos por cada 1,000 enfermos adultos en un día dado.

9. La operación de Monaldi, según se comunicó, sólo se ha ejecutado 295 veces; la lobectomía, 92.

10. En 1934 un promedio de 20 por ciento de los enfermos adultos en las instituciones americanas eran objeto del colapso en alguna forma como tratamiento de la tuberculosis pulmonar; esta proporción alcanzó un máximo de 51 por ciento en 1939, y bajó a 48 por ciento en 1941.

11. La mortalidad de los enfermos mientras se encontraban en las instituciones promedió 19 por ciento de todas las bajas durante el quinquenio 1937–1941, permaneciendo prácticamente constante; fué mínima (13 por ciento) en el grupo del Oeste, y máxima (26 por ciento), en la región de Nueva Jersey. En

Inglaterra, durante el quinquenio 1934–1938, en las "instituciones residenciales aprobadas" que trataban un número igualmente numeroso de enfermos, la mortalidad fué idéntica: 19 por ciento.

12. Aun actualmente más de la mitad de todos los casos de tuberculosis pulmonar que ingresan en las instituciones de Estados Unidos ya se encuentran en un período muy avanzado de la enfermedad cuando son recibidos por primera vez; la proporción ha continuado algo semejante, a saber, entre 50 y 57 por ciento desde 1925, cuando se ejecutó la primera encuesta nacional.

13. Considerando el cuadro en conjunto, la mortalidad de los enfermos en los hospitales y sanatorios para tuberculosis ha permanecido idéntica desde que se aplicó la colapsoterapia en gran escala, comparado con lo que sucedía en Estados Unidos durante todo el período anterior a 1931. La evolución natural de la tuberculosis pulmonar continúa sin modificar.

14. El mayor valor de los hospitales y sanatorios para tuberculosos consiste en la segregación de casos infecciosos y la prevención de la propagación de la infección en la colectividad. El tratamiento sanatorial no ha merecido toda la atención que merece; muchos de los enfermos recibidos se encuentran en la última etapa de la enfermedad, y demasiados de ellos abandonan la institución en oposición al consejo recibido después de una estancia inadecuada. En casos seleccionados aislados, ciertas operaciones quirúrgicas obtienen resultados notables que salvan algunas vidas; demasiado a menudo, otras medidas de colapsoterapia, por desgracia, añaden complicaciones a casos ya graves; la postasistencia no significa nada hoy día para la mayoría de los enfermos dados de alta, que demasiado frecuentemente deben volver a vivir y trabajar en condiciones desfavorables.

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INSTITUTIONS INCLUDED IN SURVEY (101)

Canadian (11): Fort Qu'Appelle Sanatorium; Saskatchewan Sanatorium; Prince Albert Sanatorium, Saskatchewan; Manitoba Sanatorium; Lac Edouard Sanatorium; Laurentian Sanatorium, Quebec; Mountain Sanatorium; Queen Alexandra Sanatorium; Toronto Hospital (Weston), Ontario; St. John Tuberculosis Hospital, New Brunswick; Nova Scotia Sanatorium, Nova Scotia.

New England (6): Boston Sanatorium, Rutland State Sanatorium, Middlesex County Sanatorium, Westfield State Sanatorium, Massachusetts; Shelton State Sanatorium, Norwich State Sanatorium, Connecticut.

New York City (10): Bellevue Hospital Tuberculosis Service; Sea View Hospital; Metropolitan Hospital; Riverside Hospital Tuberculosis Service; Kingston Avenue Hospital Tuberculosis Service; Kings County Hospital Tuberculosis Service; Montefiore Hospital Tuberculosis Service; Montefiore Country Sanatorium; St. Anthony's Hospital; Municipal Sanatorium.

Upstate New York (32): Grasslands Hospital Tuberculosis Service; Nassau County Sanatorium; 30 County and Municipal Tuberculosis Hospitals.

New Jersey (7): Hudson County Tuberculosis Hospital; Essex Mountain Sanatorium; Bergen County Hospital Tuberculosis Service; Valley View Sanatorium; Bonnie Burn Sanatorium; New Jersey Sanatorium; Roosevelt Hospital.

Mid-Atlantic, Southern (9): State Sanatorium, Cresson; State Sanatorium, Hamburg; State Sanatorium, South Mountain, Pennsylvania; Maryland State Tuberculosis Sanatorium; Maryland Tuberculosis Sanatorium, Henryton; District of Columbia Tuberculosis Sanatorium, Glenn Dale, Maryland; Catawba Sanatorium, Virginia; North Carolina Sanatorium; Veterans' Administration, Oteen, North Carolina.

Central Inland (7): State Sanatorium, Tom Greene, Texas; Eastern Oklahoma State Sanatorium; Waverley Hills, Kentucky; Robert Koch Hospital, State Sanatorium, Missouri; Cleveland City Hospital Tuberculosis Division; Hamilton County Tuberculosis Sanatorium, Cincinnati, Ohio.

Northern Midwest (11): Herman Kiefer Hospital Tuberculosis Service, Detroit; Maybury Sanatorium; American Legion Hospital, Battle Creek; State Sanatorium, Howell, Michigan; Chicago Municipal Sanatorium; Cook County Hospital Tuberculosis Department, Chicago; Cook County Tuberculosis Hospital, Oak Forest, Illinois; Muirdale Sanatorium, Wisconsin; Glen Lake Sanatorium, State Sanatorium, Minnesota; State Tuberculosis Sanatorium, North Dakota.

Western (8): Fitzsimons General Hospital; National Jewish Hospital, Colorado; State Tuberculosis Hospital, Salem Oregon; Pottenger Sanatorium; Weimar Joint Sanatorium; Olive View Sanatorium; Los Angeles County Hospital Tuberculosis Service; Veterans' Administration San Fernando, California.

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(3) Drolet, G. J.: Tuberculosis hospitalization in the United States, Am. Rev. Tuberc., 1926, *14*, 600.

(4) Whitney, J. S.: Tuberculosis hospitalization in the United States, Natl. Tuberc. Assn., September, 1933.

(5) Drolet, G. J.: Consolidated Statements, Tuberculosis Sanatorium Conference of Metropolitan New York, N. Y. Tuberc. & Health Assn., 1937.

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EDITORIAL

Collapse Therapy

Without an imagination there is no genuine enthusiasm in submitting a brief though deliberate clinical commentary to the article *Trends in Frequency and Type of Surgical Procedures in the Treatment of Pulmonary Tuberculosis.* A reviewer may offer to concur completely with an author's views or conclusions; he may violently disagree with his opinions; or finally, the reviewer may artfully avoid both Scylla and Charybdis. The task I have set myself is to dispel some of the impressions that one obtains in reading Mr. Drolet's article. In fact, in June, 1942 at Atlantic City, where in a slightly different form this provocative paper was presented, I was compelled to do therapeutic justice to the subject although originally I had no intention to discuss it.

The general attitude the clinician must assume towards the bewildering figures presented by Mr. Drolet is not against error—for those who know him will insist his figures are trustworthy—but rather it must be against the disposition towards confusion. Under ordinary circumstances a tape-measure is a precise tool yet to the navigator it is valueless in ascertaining the distance between one point of land and another. Perhaps the training of a statistician develops a mental pattern which holds to that which is "prescribed and recoils from the new and untried." Should one remain with the "Art of Curing Disease by Expectation;" or, in the struggle for better therapy, should one disregard the prevailing mortality index and aim at increasing the number of patients permanently arrested? To me it is quite evident that real progress insists upon both tendencies—conservative and radical—held in equilibrium. Even the celebrated Percival Pott, when discussing tuberculous spondylitis, mistakenly denied the assistance towards cure which could be found in mechanical means. It is noted then that known conservatism gave way to what was thought to have been definite radicalism.

Drolet rocks us from our complacency and perhaps fortunately so; he attempts to replace our clinical experience by mathematics. However, what must be the reviewer's interpretation of this statistical report? Mr. Drolet does not indicate that collapse therapy is unavailing, for both he and we know differently. Perhaps, his implication is that collapse therapeutic measures have been improperly or inadequately applied as to time, procedure or both. With this thought one will not take violent issue. I should like to revert to an article written by Mr. Drolet.[1] In that presentation he writes, "Recently Frost[2] suggested very thoughtfully that 'a careful review of the history of almost any infectious disease will show that in each generation, even in each decade, as knowledge and understanding have grown, ideas as to the efficacy of control

[1] DROLET, GODIAS J.: Present trend of case fatality rates in tuberculosis, Am. Rev. Tuberc., 1938, *37*, 125.

[2] FROST, N. H.: The epidemiology of tuberculosis as bearing upon its control, Thirteenth Fall Meeting, Eastern Section American Sanatorium Association, New York City, October 30, 1936.

measures have had to be readjusted. In each period measures of control which seemed appropriate have been either overestimated or underestimated.'" To-day, as always, surgeons are reshaping their principles of treatment, thereby obtaining better results. The basic purpose of this or any other estimate or critique is to disclose facts and surely not to reveal appearances. We must replace impressions with facts.

Mr. Drolet seems to convey a very unhealthy impression which is effaced if, amongst other readings, one acquaints himself with the papers delivered in 1941 at Toronto before the members of the American Association of Thoracic Surgeons. Ralph Adams reported "241 consecutive cases of thoracoplasty chosen from 4,388 consecutive admissions to the Rutland State Sanatorium, Rutland, Massachusetts." Sputum conversion occurred in 65.2 per cent following thoracoplasty. George F. Skinner discussed 226 cases operated upon between 1925 and the end of 1940. Of the earliest 21 cases, 57 per cent are apparently cured. Of the recent 126 cases (1936–1940) 58 per cent are apparently cured. R. H. Dieffenbach listed 100 cases coming to thoracoplasty (22 of whom had a revision); 78 per cent of these patients had converted sputum. G. G. Finney published 104 cases. Of these, 76 per cent were arrested, apparently arrested or improved. The last group "are for the most part patients who have been operated upon within the past year or who still have positive sputum at times." H. Meltzer in submitting his experiences with thoracoplasty (181 cases) relates, "negative sputum has been achieved in 79 per cent of the entire series. (These have been negative for at least six months.)" A. M. Vineberg (Thoracoplasty in Bilateral Pulmonary Tuberculosis) lists 49 cases and reports "42.5 per cent are well, have a negative sputum and are able to work." A. Aufses reports the results in 90 consecutive thoracoplasties for pulmonary tuberculosis. Seventy-one per cent of the cases have become arrested.

We are, then, confronted by two apparently contradictory observations: (*1*) Mr. Drolet's statistics, showing that "case fatality rates" have not declined with an increased use of collapse therapy; (*2*) the unanimous clinical observation that collapse therapy restores many patients to health and economic independence. How can this apparent paradox be resolved?

It should be emphasized that Mr. Drolet has not presented true case fatality rates of patients treated by pulmonary collapse, but rather of a large group of patients with pulmonary tuberculosis, some of whom had a variety of collapse procedures. Only institutional deaths are counted, and they depend among other factors on the duration of hospitalization. The figures do not reveal what percentage of deaths occurred in patients submitted to collapse therapy. A constant "case fatality rate" may, for example, prevail if the results of collapse therapy on carefully chosen patients steadily improve (as they probably do) and if, at the same time, the fatality rate increases in patients in whom collapse indications are pushed beyond the limit of safety.

One may well question whether the statistics presented by Mr. Drolet are at all suitable for deductions as to the efficacy of any treatment, and whether deductions from such studies can in any way alter opinions based on strictly clinical studies. Mr. Drolet's figures are of great interest to show what they

show: how the various collapse measures are being employed in different centres of tuberculosis work and, most importantly, how great the differences are in the choice of procedures, indicating that we are still, in some measure, in the experimental or developmental stage of collapse therapy.

The indications for different surgical measures have varied very widely among surgeons. This is true not only in the treatment of pulmonary tuberculosis but also, as we shall see, it has been decidedly so amongst other diseases. One must not go back many years to remember the list of indications for cholecystostomy; to-day, except in rare instances, most surgeons perform cholecystectomies. In the treatment of pulmonary tuberculosis and pyloric ulcer, I think there is an even closer analogy; in each condition the physician recognizes the relationship of surgery to nonoperative procedures; in each, however, the physician still fails to agree upon what are conservative operative measures and what are radical operative procedures. In the early days of gastric surgery a gastro-enterostomy was almost always performed for ulcer; to-day, a subtotal gastrectomy is employed. And so it will be with pulmonary tuberculosis: when a tried and proved procedure such as a "serious" thoracoplasty is used with proper indications then the case fatality rate will fall. This leads me to relate that as surgeons we are interested primarily in the number of cases arrested or cured and secondarily in the case fatality rate. It is not how many patients succumb in spite of active treatment but rather how many patients do we restore to a useful life.

To be sure, for a time medical science was groping and feeling its way with collapse therapy; one procedure and another and then still another has been submitted to the acid test of clinical experience. Procedures are scrutinized as to simplicity and results. At the moment, we can say that artificial pneumothorax therapy and phrenic nerve operations are in the main being used less frequently; also it can be related that more and more thoracoplasties are being peformed. Still the master stroke of surgery evades us! As Mr. Drolet has shown, patients still die from the ravages of the tubercle bacillus. One can be reminded that the pleasant courtship and honeymoon of collapse therapy have passed; now the crabbed laundress or seamstress of details will arduously clean up the unanswered parts or bind the unsolved loose ends of therapy. An absolute procedure is not at hand. This is an end devoutly to be hoped for but not to be obtained. Some of us, novices with the use of cavernostomy, lobectomy and pneumonectomy in pulmonary tuberculosis, look to still better results.

At the first blush it would appear that Mr. Drolet's article negates the value of collapse therapy. However, upon the basis of personal communications, I may indicate that Mr. Drolet himself would be the last one to so argue. The presentation is very worth while since it will induce the surgeon and the phthisiologist to support a detailed classification of the disease, thereby obtaining more exact indications for therapy. Those who are adverse to or blind to surgical therapy will embrace it when surgeons are bold enough to perform reasonable, radical surgery. Such are the reactions of bewildered short-sightedness. It is just as well perhaps that our complacency has been jolted.

LOUIS R. DAVIDSON

STATISTICAL DATA

Edited by MARY DEMPSEY

WARTIME INCREASES IN TUBERCULOSIS DEATH RATES

Numerous foreign publications are now available which contain articles discussing fairly general increases in the 1941 deaths from tuberculosis which have occurred in some of the countries at war. As one British authority[1] states: "Mortality figures cannot be taken as a measure of the incidence of the infection without criticism, but they are the only statistics available which approach any degree of accuracy." This statement is peculiarly true during this war period since it is possible that in the third year of the war the population may have been lessening by civilian migration and by foreign assignment of the armed forces. The lack of information regarding population movements makes it difficult to evaluate the rising number of deaths in terms of rates.

England and Wales: Between 1939 and 1941 the number of tuberculosis deaths in England and Wales increased 12 per cent, according to Dr. Percy Stocks,[2] Medical Statistical Officer for England and Wales. While deaths from tuberculosis of the lungs had increased 10 per cent in 1941, as compared with 1939, tuberculous meningitis led to an excess of 40 per cent in the number of deaths recorded last year.

Deaths from tuberculosis, classified by type of disease
England and Wales, 1939-1941

TYPE OF DISEASE	DEATHS FROM TUBERCULOSIS OCCURRING IN—		
	1941	1940	1939
All forms	28,670	28,144	25,623
Tuberculosis of the respiratory system	23,634	23,660	21,542
Tuberculous meningitis	2,366	1,886	1,684
Other forms of tuberculosis	2,670	2,598	2,397

Abnormal war conditions are blamed for this increase in the number of deaths from tuberculosis which is of special interest because the general death rate (from all causes) has not advanced noticeably in England and Wales. The subsequently reversed policy of closing tuberculosis hospitals in the early days of the war and of sending infectious patients home must be held responsible for much of the increased mortality. Under these less favorable conditions many of those patients already ill died earlier than they might have done otherwise; in addition, they inevitably spread the infection among their families. In fact, 1941 deaths from tuberculosis among children under ten years of age were 45 per cent in excess of those in the same age group in 1939.

[1] Frederick Heaf and Lloyd Rusby: A Further Review of Tuberculosis in Wartime, Tubercle, May, 1942, p. 107.

[2] Percy Stocks: Vital Statistics of England and Wales in 1941, British Medical Journal, June 27, 1942.

All these findings indicate that English and Welsh children have been coming more and more in contact with open cases of the disease, while at the same time their resistance was being lowered by change in diet, unaccustomed environment, poor milk, lack of sleep and inadequate rest due to double summer time. No doubt much of the rise is directly traceable to shelter life and the careful precautions taken against air raids. Moreover, the shortage of physicians and nurses has become extremely serious.

The percentage of increase in number of tuberculosis deaths from 1939 to 1941 is twice as high as the increase which occurred between 1914 and 1916, the corresponding period of the first world war. Moreover, no comparable advance was noted in the first war period with reference to tuberculosis deaths among young children. During the first war, bombardment by air had not been developed to such a point as to require frequent retreat to shelters where the spread of the disease is so readily facilitated.

In 1940, tuberculosis deaths in England and Wales increased 10 per cent over the preceding year whereas in 1941 a further advance of 2 per cent was noted. To what extent this lessened advance may be attributed to population changes in 1941 it is impossible to state.

A signed article in the May issue of *Tubercle*[1] mentions a 50 per cent increase in deaths from tuberculosis among mental patients between 1938 and 1940, even though the number of admissions to mental hospitals had declined somewhat during this period. The rise in this group is of interest since these patients are not subjected to long hours and strain incident to industrial fatigue; on the other hand, part of the facilities in mental hospitals were taken over for war service with the result that such institutions were overcrowded.

Scotland: Deaths from tuberculosis in Scotland increased at an even higher rate than in England and Wales.[1] Between 1939 and 1941 this rise was 18 per cent. In this country deaths from tuberculous meningitis in 1941 were 50 per cent in excess of those in 1939, while deaths from pulmonary tuberculosis advanced 15 per cent during the same period. It is conceivable that by 1941 the population of Scotland may have increased as a result of migration from England but the authors of the article in question do not mention that possibility.

Paris: Dr. Ramon F. Minoli[3] in a recent article discusses mortality in Paris with reference to the food rationing there. He finds that tuberculosis deaths in the first six months of 1941 had increased 10 per cent as compared with deaths in the first half of 1939. Among children from one to nine years of age the rise in this period was 28 per cent.

The Census of 1936 indicated that Paris had at that time a population of 2,830,000. From the number of food ration cards issued in the Fall of 1940, it seems evident that the population had decreased by 400,000. This 14 per cent decline in the city's population makes the increase in tuberculosis deaths doubly significant.

During the first eleven months after food rationing began in October, 1940, Doctor Minoli reports an increase of 21 per cent in the mortality from all causes

[3] Ramon F. Minoli: Food Rationing and Mortality in Paris, 1940–1941, The Milbank Memorial Fund Quarterly, July, 1942, p. 213.

among persons sixty years and over, as compared with an average covering the same months in the preceding four years; this rise was especially marked during the winter months. In general, however, the number of deaths among all persons under sixty years showed no advance.

Requests for sputum examinations in Paris laboratories were not only greatly increased, but the proportion of positive results showed a pronounced change. Doctor Minoli gives the average figures from five laboratories as follows:

1938— 54.3 positive results per 1,000 sputum examinations
1939— 59.1 positive results per 1,000 sputum examinations
1940— 72.2 positive results per 1,000 sputum examinations
1941—211.0 positive results per 1,000 sputum examinations

In addition, competent authorities have observed an increase in the proportion of cases of rapidly developing fatal tuberculosis.

A careful survey[4] made in the early summer of 1941 indicates that the diets of Parisians represented:

1. A total caloric insufficiency of about a thousand calories daily.
2. A calcium deficiency and a calcium-phosphorus imbalance.
3. An insufficient amount of vitamin A.

This survey was based not on rationed food but on the *total* food consumed by 65 families whose homes were visited by specially trained nurses each day for a week. These nurses weighed all food (rationed and otherwise) which was consumed by male and female members of the 65 families who were between the ages of twenty and fifty years.

Doctor Minoli concludes: "If the present dietary régime continues and the consequences increase, the problem of tuberculosis in France will be exceedingly grave."

Canada: The September bulletin of the Canadian Tuberculosis Association announces an increase of 5 per cent in the number of deaths from tuberculosis among Canadians in 1941, as compared with those in 1940. These figures represent the first appreciable increase in fifteen years. In other words, the Canadian death rate advanced from 50.6 in 1940 to 53.1 in 1941.

Germany: Unconfirmed but frequently repeated press reports emphasize a pronounced recent increase in the incidence of tuberculosis, diphtheria and scarlet fever in Germany. Detailed reports signed by accredited physicians or statisticians covering vital statistics in Germany for the past year or two are not available.

United States: Final figures, recently issued by the U. S. Bureau of the Census, show a tuberculosis death rate of 44.4 per 100,000 population in 1941. This figure represents a slight decline from the rate of 45.9 in 1940.

Preliminary data for the early months of 1942 imply that the slight decline in the death rate may be continued in the first year of America's participation in the war. A very different figure may result, however, if the war should last several years and if citizens of the United States should be subjected to conditions which approximate those now prevailing in England.

[4] Survey made by H. Gounelle and R. Mande of the Institut des Recherches d'Hygiene.

BOOKS

LEOPOLD LICHTWITZ: *Functional Pathology. Pp. xiv + 567, with 157 figures and 39 tables, New York, Grune & Stratton, 1941, cloth, $8.75.*

By TINSLEY R. HARRISON

In the preface to this volume the author states, "It is deliberately written from a very personal viewpoint; on many occasions it does not harmonize with widely accepted—or what has been termed orthodox—opinion. It should therefore stimulate discussion."

This is the greatest virtue of the book, namely, that it is written from a personal point of view and that it does, in certain respects, controvert established concepts. However, the value of an idea should not be judged by its orthodoxy but rather by the evidence upon which it rests and, using this as a criterion, many of Doctor Lichtwitz's unorthodox ideas would seem to be sound.

The most striking general impression which the book makes on the reader is the revelation of the breadth of the author's knowledge and interests. The author shows himself to be a profound student of embryology, anatomy, chemistry, physiology and clinical medicine. Doctor Lichtwitz is evidently a true student of human biology.

The book covers progressively the functional pathology of endocrine disorders, the general regulation of metabolic processes, a detailed discussion of certain specific metabolic processes, discussion of immunity and consideration of functional pathology of the blood, cardiovascular, renal and hepatic systems. All parts of it are good but—as in all books—some parts are better than others. The best portions are, in the reviewer's opinion, those chapters which deal with the regulation of metabolism. The author is inclined to place much stress on the hypothalamus—more than most authors would think justifiable. However, one has to grant that the researches of recent years lend strong support to his point of view. The reader will have to search far to find discussions of heat regulation, regulation of metabolism, body water and carbohydrate metabolism as clearly presented as are the discussions in Doctor Lichtwitz's book. I know of no other volume which applies so directly to disease the recent advances in the study of intracellular oxidations.

It may be worth while to point out some of the specific items in which the author's point of view is widely at variance with currently accepted concepts. He states, for instance, that in certain patients with nephrosis, the hyperproteinaemia and hypercholesterolaemia may precede the albuminuria. He believes that in such patients the oedema may be the result of primary disturbance in the hypothalamus rather than in the kidney. He makes contradictory statements such as the one on page 162, in which he states that in thyrotoxicosis the increase in cardiac output does keep pace with the increase in basal metabolic rate, and a few lines later states that arteriovenous difference and oxygen content are small and the venous blood relatively rich in oxygen.

At times the author goes rather far into speculation. Thus, on page 394, he makes the statement that the kidney may have a double effect on blood pressure, the one a chemical and the other a nervous effect. Although there is certain clinical evidence supporting the latter mechanism, there is little or no experimental evidence to support it, and the author does not cite the evidence on the two sides of this question.

These faults are, however, quite minor. The important thing is that Doctor Lichtwitz has written an extraordinarily clear and concise presentation of certain fields of functional pathology and brought together in one volume much information which can be found in no other single book, but which the reader would otherwise only come upon by searching almost endlessly through many hundreds of papers in the literature. The volume combines breadth and depth to an unusual degree and everyone interested in the mechanism of disease will profit from reading the book.

JULIUS BAUER: *Constitution and Disease. Applied Constitutional Pathology. Pp. ix + 208, New York, Grune & Stratton, 1942, cloth, $3.50.*

By GEORGE C. LEINER

As the author states in the preface, this book originated from lectures given at the University of Vienna between 1923 and 1938.

Modern medicine overstresses the importance of exogenous factors in the origin of diseases and the constitutional factor is for the most part neglected. Constitution is defined as the sum total of an individual's characteristics, as they are potentially determined at the moment of fertilization. A constitutional trait is abnormal when it is found in less than 4.5 per cent of all individuals. Constitution plays a rôle in the aetiology of diseases, it is a modifying factor of the clinical picture and of the course of disease, and it should be taken into account when therapeutic measures are undertaken. Certain organs and tissues may in different individuals show a biological inferiority and, therefore, be *loci minoris resistentiae*. The endocrine system and the nervous system act as integrative systems of the individual constitution.

Various forms of abnormal constitution are pointed out. Persons with one habitus show a greater frequency of certain diseases than others. Diseases considered to be chiefly constitutional in aetiology are: diabetes mellitus; obesity; essential hypertension; pernicious anaemia and iron deficiency anaemia; haemolytic anaemias (sicklaemia, ovalocytosis, spherocytosis); erythraemia and leucaemia; Hodgkin's disease; haemorrhagic diatheses (haemophilia, pseudohaemophilia); peptic ulcer; cancer.

It is not enough to make a correct diagnosis; the patient's whole personality should be understood. Although a disease has been recognized as constitutional, therapeutic results can be achieved. The value of psychotherapy is stressed. Cases from the author's own experience illustrating the various problems are reported.

The bibliography does not comprise the entire literature on the subject, as the author himself says. His works and the works of his coworkers are more frequently referred to. The book is written clearly and in a fascinating manner. Its content and point of view are stimulating, as were the author's former books and his lectures in Vienna.

RALPH H. MAJOR: *Physical Diagnosis. Second Edition, revised. Pp. xiv + 464, with 437 illustrations, Philadelphia and London, W. B. Saunders Company, 1940, cloth.*

By SOL BILOON

This is a text for an introductory course in physical diagnosis. The author's enthusiasm for the subject and his scholarship make this volume very pleasant reading. There is enough historical background in the text to capture the interest of the reader. There is also a genuine attempt to explain, whenever possible, the mechanism of production of the physical sign under discussion.

The illustrations are abundant and of very high quality. Instrumental methods such as X-ray and electrocardiography are not discussed at length but the text gives the proper place and weight to these diagnostic aids.

This book is recommended not only as an excellent text but also as an inspiration to medical students.

F. DENNETTE ADAMS: *Cobot and Adams Physical Diagnosis. Pp. xv + 888, with 398 figures, The Williams & Wilkins Company, Baltimore, 1942, cloth, $5.00.*

By SOL BILOON

This standard text on physical diagnosis is now in its 13th edition. This book is unusually complete, with adequate discussion of instrumental aids in diagnosis and with excellent chapters on neurological and orthopedic examination. The text is easy to read and the significant matters are in heavy type.

The original point of view of Doctor Cabot with respect to examination by systems, expressed in the preface to the first edition, is maintained in this edition. The data obtained by laboratory examinations and by the use of instrumental methods are considered as essential parts of any medical examination and are integrated with the data obtained by the unaided senses. No special dignity is given to any sign because of its source. This point of view is not commonly expressed in medical literature and it is an excellent thing to teach it in a course in physical diagnosis.

This book is highly recommended.

ELMER B. MODE: *The Elements of Statistics. Pp. xvi + 378, Prentice-Hall, Inc., New York, 1942.*

By GEORG WOLFF

Although there is certainly no lack of textbooks in statistics, the new book of Professor Mode deserves recommendation as a very clear introduction to all students who are looking for a more general and yet comprehensive treatment of the elements in mathematical statistics. The examples in the text are mostly taken from vital statistics, anthropology and economics. It seems to the reviewer to be an advantage of the book that for the same sample, for example, head lengths of 462 English criminals, the various methods of computing the most used statistical characteristics are demonstrated. Thus the mean values in a set of variates (arithmetic, harmonic, geometric mean, median, mode) are discussed on hand of the same sample; the like the usual measures of dispersion (mean deviation, standard deviation, coefficient of variation, quartile deviation), their meaning for the frequency distribution of the observational data and their mathematical properties. The simplest way to compute these constants is always shown and how to shorten unnecessary calculation work. There are, of course, further included some chapters on more advanced items, such as index numbers, moments, curve fitting, correlation methods. The special chapter on the frequency curve (probability curve) is excellent, showing the fundamental meaning of this function in all statistical and probability problems. The conception of probability is already introduced in an early chapter on simple statistical problems and continued throughout the text up to the last chapters which deal with the binomial distribution of frequencies; here also some elementary theorems on permutations and combinations are discussed in an easy mathematical way which characterizes the whole book. As the author points out in his preface, the book presupposes no mathematics beyond the usual secondary-school geometry and algebra. However, as holds true for every good textbook on applied mathematics, the reading and enjoying of the clear-cut definitions will also require some collaboration on the part of the reader who is greatly aided by a series of examples worked out in the text and a great many of exercises for solution at the close of each chapter. Also the use of the slide-rule is explained in an introductory chapter (usually left out in routine textbooks), which will prove helpful to many students and remind them of the useful application of a mechanical logarithmic system before using the calculation machine. The text closes with a chapter on measures of reliability, sampling theory and the manifold use of the standard error in statistical evaluations. Finally the much employed Chi-square test is here briefly discussed and demonstrated. This final chapter might be well enlarged and supplied with some more examples in a future edition, since this reliability test (goodness of fit) has found more and more application in medical and psychological research, laboratory and statistical surveys. A very useful set of separate tables completes this well written and well printed textbook.

DOROTHY B. NYSWANDER: *Solving School Health Problems. Pp. xii + 377, New York, The Commonwealth Fund, 1942, cloth, $2.00.*

By LOUIS E. SILTZBACH

Our schools are strategically placed to set the child on the road to good health and good health habits. They strive to do so. Yet nearly everyone is agreed that present school-health programs fall far short of this goal. Many surveys have shown that the hunt for physical defects in the children, at admission to school and sometimes at graduation, is not enough. What is lacking is an organized effort to educate the teacher, the child and, above all, the parent, as to the significance of any health problem discovered and the means of solving it intelligently.

This book is an excellent blueprint for a program to accomplish just that.

The Department of Health and the Board of Education of New York City undertook an intensive four-year study of the health practices in the schools of the Astoria Health District. Their findings and the recommendations that grew out of them are recorded here.

The investigators took nothing for granted. Every procedure was put under the microscope, analyzed, changed and changed again, until the practice of the activity yielded the results that the theory underlying it had projected. The place of parent, teacher, school nurse, school physician, family physician, clinic and hospital and other persons involved in school health activities was mapped out and, where necessary, rearranged to give maximum results to the combined effort of all.

Included are special sections on visual acuity, loss of hearing, dental problems and management of the cardiac school child. There is no discussion of the tuberculous child. The investigation brought about modification of records, integration of relationships among teacher, nurse, parent and school physician, and readjustment of physicians' and nurses' working schedules. Noteworthy is the book's discussion of the means of furthering rapport between the family physician and the school personnel. The plan here evolved has wide applicability, for all suggested procedures can be adapted to local conditions where necessary. This is a "must" book for all those who are in any way involved in school health work.

ANNE MARIE SMITH: *Play for Convalescent Children in Hospitals and at Home. Pp. xviii + 133, A. S. Barnes and Company, New York, 1941, cloth, $1.60.*

By MILDRED S. HAMILTON

The layman and the professional hospital worker have been and are becoming increasingly conscious of the necessity of treating the sick person as a "whole" and not as an isolated disease. In considering the convalescent child this little book offers further proof of the great need for understanding the child's emotional and intellectual make-up as well as his physical disability.

With play activities well organized, any children's unit can be made into a happy and constructively busy place. The practical suggestions offered are excellent and should be helpful to nurses, occupational therapists and to hospitals which have untrained volunteers working on the children's wards. The activities described have been utilized over a period of time at The Children's Memorial Hospital in Chicago and have proved most satisfactory. Despite the inclusion of too many minor details of this particular play organization, and a rather large number of wordy but sincere testimonials by student nurses, etc., the value of the material is such as to warrant consideration by hospital superintendents and medical directors seeking to meet the needs of hospitalized children.

Books Received

ALBERTO CHATTÁS: La Vacunación Antituberculosa con el B.C.G. Pp. 264, Imprenta de la Universidad, Cordoba, República Argentina, 1942, paper.

Facts that Tuberculosis Patients Should Know. Prepared and edited by Jacob Segal, John Cahill, Joseph Hartman, Gladys M. Park and Gladys A. Adams. Pp. 19, published by the Bronx Tuberculosis and Health Committee of the New York Tuberculosis and Health Association, Inc., Bronx, New York, 1942, paper.

Mecanismos de Acción de la Terapéutica Antituberculosa. Volume IV of Publicaciones del Instituto Antituberculoso "Francisco Moragas", Barcelona, 1941, pp. 183, paper.

Publicaciones del Centro de Investigaciones Tisiologicas. Volumen V. Director: Prof. Roque A. Izzo. Pp. 388, Pabellon "Las Provincias," Hospital Tornu, Buenos Aires, 1941, paper.

AMERICAN TRUDEAU SOCIETY

Report of the Mississippi Valley Trudeau Society

Dr. H. S. Willis, *Secretary*

The 1942 meeting of the Mississippi Valley Trudeau Society convened at the Edgewater Beach Hotel, Chicago, Illinois, on September 17 and 18, 1942, with a symposium on *Industrial Work* and a section on *Tuberculin Test and Tuberculosis Control.* The joint afternoon session and the two sessions the following day were well attended and were featured by the presentation of several unusually valuable contributions. Particularly timely were the papers on *Pulmonary Pathology in an Army Camp, Chest Surgery in War* and *Experimental Work on Response to Blast.* The evening X-ray conference under Doctor Skavlem's able direction was a very successful meeting.

The President named the following members to the Nominating Committee:

Dr. James F. Busby
Dr. R. H. Runde
Dr. O. A. Sander

This Committee submitted the following suggested roster:

President—Frank L. Jennings, M.D.
President-Elect—H. S. Willis, M.D.
Vice-President—J. B. Novak, M.D.
Secretary-Treasurer—John A. Skavlem, M.D.

At the business meeting the Committee on Constitutional Revision, under the Chairmanship of Dr. George C. Turner, made a report in respect to membership. This report was read and will be voted on at the next meeting.

The meeting was well attended. Interest was active and acute despite the country's war effort.

AMERICAN TRUDEAU SOCIETY

Report of the Southern Trudeau Society

Dr. Julius Lane Wilson, *Secretary-Treasurer*

The Southern Trudeau Society met with the Southern Tuberculosis Conference in Memphis, Tennessee, on October 5, 6 and 7, 1942. Although there were physicians present from every state in the Southern Conference area, the attendance was small due to war-time travel.

The program was dominated by the problems of tuberculosis control among civilians and service men in war. There were also excellent papers on the surgical treatment of tuberculosis, tracheobronchial tuberculosis, and tuberculosis among Negroes.

Twenty-nine members attended the luncheon meeting on October 6. The new constitution of the Southern Trudeau Society was adopted and the following officers were elected:

Dr. Horton R. Casparis, President
Dr. Duane Carr, Vice-President
Dr. Julius Lane Wilson, Secretary-Treasurer

Dr. Victor F. Cullen, presiding, spoke eloquently of the past history of the Southern Association Organization, and Doctor Casparis gave a challenging talk on the need for deeds rather than words in the present crisis.

Announcement

The American Board of Internal Medicine

Pursuant to the policy of the American Board of Internal Medicine to keep fees at a minimum consistent with efficient function of the Board, it is now possible to reduce the registration and examination fee. Accordingly, the following action has been directed:—The registration and examination fee will be reduced from forty dollars to thirty dollars. The certificate fee will remain at ten dollars, making a total of forty dollars. The oral examination fee in the sub-specialties will remain at ten dollars.

This reduction in fees will become effective as of January 1, 1943, and will apply to candidates for the written examination on February 15, 1943 whose applications have not been accepted for a previous examination.

ERNEST E. IRONS, M.D.
Chairman

CARDIAC SYMPTOMS IN PERSONS WITH DISTORTION OF THE MEDIASTINUM DUE TO PULMONARY TUBERCULOSIS[1]

A Report of Thirty-eight Cases

DANIEL M. BRUMFIEL

This article attempts to bring more nearly up to date this subject upon which the author published a preliminary report in 1933 (17). Follow-up data have been available on some of the cases originally reported and additional cases observed to the total number of 38 in the period ending February 1, 1941. The conclusions previously drawn have been reappraised in the light of this somewhat amplified experience and from the published statements of other observers. This accumulated weight of evidence supports the author's earlier contention that distortion of the mediastinal structures *per se* may give rise to cardiac symptoms.

This association of ideas is not new. Babcock recorded it in 1884 (6), as did both McSherry (57) and McAldowie (56) in 1886. The sparsely scattered literature of the following decades was largely devoted to the pathological-anatomical observations on cases of acquired dextro- and sinistrocardia with detailed descriptions of the associated bizarre physical findings. The classic reports of Bard (7) and Armand-Delille *et al.* (5) stand as representative of that school of writers. The literature became suddenly augmented following the wide adoption of therapeutic pneumothorax. For the most part, the recorded observations were made upon acute displacements of the heart and mediastinum as seen in pleural effusion, spontaneous pneumothorax, massive atelectasis or the temporary visceral derangements encountered in the course of pneumothorax therapy. The possible effect of chronic or permanent intrathoracic deformities has not received the attention it deserves among American authors in spite of the early warnings of Pottenger (65, 66) and Fishberg (30).

This report deals exclusively with observations on persons with chronic, or permanent, displacements of the heart and other mediastinal organs, in whom cardiac symptoms supervened, sometimes after a long interval. In the preliminary report of 1933, the writer recorded clinical observations made on 15 tuberculous individuals with distortion of the mediastinum as a result of pulmonary disease. These observations pointed to the inference that permanent distortion of the mediastinum and its contents might produce circulatory symptoms *per se*.

The writer continues his preference for the term mediastinal "distortion" as more expressive than "displacement" or "shift." "Distortion" implies permanency and embraces all varieties of mediastinal deformities, including lateral or vertical displacements, rotation and angulation, either alone or in combination.

A few of the cases here recorded were encountered among the author's tuberculous patients. The majority were seen through the courtesy of confreres in Saranac Lake and nearby sanatoria.

[1] From The Edward L. Trudeau Foundation, Saranac Lake, New York.

CRITERIA

The criteria for classifying patients in this category were: (*1*) cardiac symptoms; (*2*) demonstrable distortion of the mediastinum by physical signs and roentgenograms; (*3*) a past medical history free from known cardiac disease or those infections recognized to affect the heart, such as the acute rheumatic infections or syphilis; (*4*) absence of the physical signs of cardiovascular disease, and absence of other concurrent disease, such as syphilis or hyperthyroidism, known to affect the cardiovascular system either organically or functionally. These criteria were as rigidly applied as the available data permitted. Thirty-eight cases conformed to these requirements.

Eleven others with distortion, including 2 of the 15 originally reported (17), were discarded because of demonstrable organic cardiovascular or concurrent systemic disease which might conceivably provide aetiology for the symptoms. These 11 were specifically: 2 with syphilis, 2 with a possible rheumatic aetiology, 2 with definite arteriosclerosis and myocarditis, one with nephritis, one with amyloidosis, one cardiovascular renal case, one with pneumonoconiosis and one who later developed definite hyperthyroidism. While these rejected cases would be subject to the same disturbing influence as the other 38 and might well be more likely to develop symptoms, all 11 are omitted in order to avoid complicating the picture.

The author well realizes the possible weakness of his position in adjudging these 38 cases to be free from organic cardiovascular disease largely on clinical data alone in this age of critical investigation. A few of the cases have been followed for several years; others were seen only once or twice, later information coming through the referring physicians or from outside sources if the cases had removed from Saranac Lake. The present status of one is unknown. Only 12 of the cases had electrocardiograms. No venous pressures were taken at the time of observation and none of the patients were subjected to modern respiratory physiological studies. Such investigations might reveal abnormalities that would indicate the presence of an otherwise nondemonstrable residual diffuse toxic myocarditis, which has so often been described in persons dying of tuberculosis. However, the studies on venous pressure and circulation time in 30 cases of displacement by Ferretti and Lentini (29) gave no useful conclusions. Even more elaborate studies were made by Fontana and Zubiani (31) on congenital and acquired dextrocardias with similar results.

CAUSE OF DISTORTION

Distortion of the mediastinum in the tuberculous may follow as the end-result of several processes, either alone or in combination. *Atelectasis* of a lobe or entire lung may occur as the result of bronchial stenosis due to tuberculous ulceration and cicatrization. Farris in 1925 (28), Ameuille and Trocmé in 1926 (3), Packard in 1928 (60), and Ruiz and Gil in 1933 (71) reported cases of atelectasis in tuberculosis. Tracheobronchial tuberculosis is being recognized much more frequently than formerly and this possible end-result is usually borne in mind. *Fixation and contraction of a thickened pleura* following effusion is a frequent cause

of intrathoracic deformities. This is commonly noted after empyema, but may also occur subsequent to long-standing serous effusions. *Fibrosis and contraction* of the pulmonary parenchyma due to tuberculosis may result in extreme and sometimes bizarre distortions. This is usually the cause of those deformities in which contraction of a fibrosed or fibrocavernous upper lobe leads to extreme displacement of the superior mediastinum as emphasized by Blanco Rodriguez (12). These distortions may be very gradual in development. Cardiac symptoms, if and when they do occur, may be so delayed and so insidious in onset that neither patient nor physician associates them with the long quiescent or arrested pulmonary disease. *Therapeutic pneumothorax*, all too often, has for one of its end-results a major displacement of the mediastinum and its contents. Even therapeutically successful cases may so eventuate if complete reëxpansion is impossible because of extensive intrapulmonary fibrosis or rigid visceral pleura. The latter circumstance is more likely when the pneumothorax is complicated by prolonged pleural effusion, especially if empyematous. In unsuccessful pneumothorax all sorts of combinations of factors are prone to occur, such as the uninterrupted fibrosis and contraction of a diseased upper lobe with the development of empyema and rigid visceral pleura at the base.

CLASSIFICATION OF DISTORTIONS

Distortions of the mediastinum may be either to the right or the left. They may involve the entire mediastinum or be predominantly limited to the superior portion. Clear cut examples of partial displacement, involving only the inferior mediastinum as reported by Harper (38) and by Swynghedauw (79), were not seen in this series. Angulation of the heart upon its great vessel anchorage may take place by extreme elevation of the apex or, as reported by Everett (27) and Heyse (42), by the apex pointing posteriorly. In addition to these easily detectable deformities, the heart may be rotated upon its vertical axis, coincident to a lateral shift of the mediastinum. This may sometimes be inferred from a shift in the electrical axis of the electrocardiogram but visual proof would depend upon outlining the chambers by some intravascular radiopaque roentgenographic technique as that demonstrated by Robb and Steinberg (69). Twenty-four of these cases showed shift to the left and 14 to the right. In 2 of the right-sided and one of the left-sided deviations the superior mediastinum had suffered more marked displacement than had the inferior portion. In one the superior mediastinum only was markedly distorted to the left. One instance of sinistrocardia was further complicated anatomically by an upward tilting of the cardiac apex by phrenic evulsion. While shifts to the left occur almost twice as often as to the right in this series, the number of cases is too small to conclude that symptoms occur more often with distortion to the left than to the right.

The physical signs are as variable as the cases themselves. Attention should be called to the frequency with which a loud systolic murmur is heard over the pulmonary conus in marked distortion of the superior mediastinum to the left and occasionally over the aorta in right-sided deformity. Particularly over the pulmonary artery this murmur may be long drawn and harsh as well as loud.

This has been the subject of considerable discussion by Génévrier and Descomps (33), Bard (7) and Cavarozzi (19). The production and character of this murmur is readily explained by the deformity—torsion or angulation—of the great vessel over which it is heard.

The "pseudo-cavitaire" phenomenon, discussed so widely in the French and Italian literature and in South America by such writers as Palacio (61), occurs almost universally when the trachea is sharply deviated to one side and in contact with dense apical pulmonary fibrosis.

CLASSIFICATION AS TO SYMPTOM COMPLEX

Any attempt to classify the patients on the basis of variations in the symptom complex must be somewhat arbitrary. By far the commonest complaint encountered was that of dyspnoea in excess of that to be expected on a purely pulmonary basis. This is admittedly difficult to estimate clinically as the bronchospirometric studies of Jacobaeus (46) and his followers have shown. Other frequent complaints were: palpitation, fast pulse or rapid heart action, weakness, ease of fatigue and various subjective experiences of arrhythmia. Pain occurred

TABLE 1

Symptomatic cardiac insufficiency	16
Symptomatic cardiac insufficiency with arrhythmia	14
Anginoid syndrome	6
Symptomatic cardiac insufficiency plus pain	1
Symptomatic cardiac insufficiency plus pain, plus arrhythmia	1

less often but, when present, was usually the major symptom. With few exceptions, the symptom complex consisted of dyspnoea, palpitation, weakness, with or without some manifestation of arrhythmia. The same combinations of symptoms have been reported by Cobet and von der Weth (23), Chassagnac (20) and Cavarozzi (19) among others. This syndrome has been called "symptomatic cardiac insufficiency" on the Medical Service of the Henry Ford Hospital, Detroit, where the author adopted the term as being apt and descriptive. It carries the full idea of the patient's subjective experience and implies the absence of the objective signs of either right or left myocardial failure. Those cases in which pain was the conspicuous feature have been classified as presenting an *anginoid* syndrome, because they suggested effort angina but were not characteristically typical of that condition. Some of these were also seen by prominent cardiologists who supported the author's opinion that the symptoms were on a mechanico-functional rather than a coronary basis.

Table 1 divides these cases into their most natural grouping by symptom syndromes.

LATENT PERIOD

One remarkable fact that comes to attention in this study is the common experience of a free interval between the establishment of the deformity and the onset

of symptoms. Clayson (22) noted this same fact in his series in 1932 and postulated that in most individuals the heart tolerated its new position well for a time. Similar comments have been made by Génévrier and Descomps (33), as well as the author (17). In the present series there were only 10 cases without this latent period. In the others the interval varied from less than one year to twenty-seven years. In nearly one-half—17 cases—the symptoms developed so insidiously that the patients were unable to even roughly date the onset. The majority of these were instances of chronic fibrosis and contraction, the condition in which the distortion is of such gradual development that it also is difficult to date. Of the 11 patients who were able to date the onset of symptoms with reasonable accuracy, one claimed a free interval of three years, one of four years, 3 of five years, 2 of six years, 2 of twelve years, one of seventeen years and one of twenty-seven years.

Thomas, Reinhoff and Allan (80), in a careful study, reported on the perfect readjustment occurring after pneumonectomy. Doubtless many individuals will adjust perfectly and, it is hoped, permanently to a marked mediastinal deformity, but in light of these observations a ten or fifteen year follow-up on these pneumonectomy cases would be instructive and convincing.

If the latent period is too long we find ourselves on controversial ground. As years pass the patient enters the age period of the degenerative cardiovascular diseases. These conditions, too, are likely to be of insidious onset and the differentiation between symptoms of organic and functional origin may not be easy. Granting the possibility of visceral distortion as a cause of symptoms, it is evident that all cases—who continue to survive—will eventually enter that age group in which degenerative diseases must be given consideration.

COMPENDIUM OF CASES

Rather than crowd these pages with a running clinical description of each case, the salient features are presented in tabular form. Here, in greatly abbreviated form, are shown: age, sex, cause of distortion, major symptom complex, objective cardiovascular abnormalities, if any, duration of symptoms, latent interval, EKG, etc., and follow-up information. Type and degree of lateral distortion are shown by outline sketch of the mediastinal shadow with reference to the vertebral column and chest wall. Solid line sketches were traced from chest films and broken line diagrams have been reconstructed from clinical notes, where films were not available.

ILLUSTRATIVE CASES

The following 5 cases are presented in greater detail. They have been chosen to illustrate each of the symptom complexes, rather than types or degrees of distortion.

Case 25: F. M., female. *Symptomatic cardiac insufficiency without arrhythmia:* This office worker, in her early forties, was being considered for thoracoplasty because of reactivation of disease in the left lung, quiescent under pneumothorax treatment for several years. The pneumothorax had been lost by the intervention of a pleural effusion two years pre-

1	A.S. - F, age 30 (1928)	S.C.I.	
	Cause - Chr.Fib.+Pnx.	Symptoms - Gradual	
	Fr.Int. - 0	Died: Progressive TB two years later	
2	A.B. - F, age 44 (1929)	S.C.I.+Arr.+Ang.	
	Cause - Chr.Fib.	Symptoms - Gradual	
	Fr.Int. - ?	EKG - 4, all normal	
	Helped by sedation (See Text)	Semi-invalided cardiac 12 years. No congestion	
3	G.C. - M, age 58 (1930)	S.C.I.+Arr.	
	Cause - Chr. Fib.	Symptoms - Gradual	
	Fr.Int. - ?	Died: Rapid congestive failure, few months later	
4	G.W. - M, age 40 (1930)	S.C.I.+Arr.	
	Cause - Pnx.	Symptoms - 3 years	
	Fr.Int. - 6 years	EKG - normal	
	Improved on sedation	Otherwise unchanged	
5	L.H. - F, age 28 (1930)	S.C.I.+Arr.	
	Cause - Pnx.	Symptoms - 8 years	
	Fr.Int. - 0	Improved on sedation and graduated exercise; well seven years later	
6	L.H.W. - M, age 37 (1931)	S.C.I.+Arr.	
	Cause - Chr.Fib.	Symptoms-Gradual	
	Fr.Int. - 0, EKG - Rt. axis dev.		
	Improved by 1st stage thoracoplasty 9 years later cardiac symptoms still improved.		
7	E.M. - F, age 34 (1931)	S.C.I.+Pain	
	Cause - Pnx.	Symptoms - 4 years	
	Fr.Int. - 5 years (See Text)	Died: Rapidly prog. TB 7 years later	

PLATE 1

8

A.G. - F, age 62 (1931) S.C.I.-Cong.Failure

Cause - Chr.Fib. Symptoms - Gradual

Fr.Int. - ? Died: 7 weeks later, congestive failure

9

J.K. - M, age 45 (1931) S.C.I.-Arr.

Cause - Chr.Fib.+Cavity Symptoms + 1 year

Fr.Int. - ? Improved on sedation
Died: Unrelated cause

10

H.R. - M, age 28 (1932) S.C.I.

Cause - Chr.Fib.+Pnx. Symptoms - Gradual

Fr.Int. - ? Died: TB, 6 years later

11

M.D.E.-F, age 34 (1932) S.C.I.

Cause - Chr.Fib.+1st stage thoracoplasty Symptoms - Sudden post op.

Fr.Int. - O Died: Progressive TB
See the type death

12

J.M. - M, age 44 (1932) Ang.

Cause - Chr.Fib.+Cavity Symptoms - 1 year

Fr. Int. - 1 year Seen pre.op.

Died: Progressive TB after operation

13

V.H. - M, age 36 (1932) S.C.I.+Arr.

Cause - Pnx.+Empyema Symptoms - 8 years

Fr.Int. - O Still cardiac semi-invalid
(See Text)

14

L.C. - F, age 36 (1932) S.C.I.+Arr.

Cause - Chr.Fib. Symptoms - 2 years

Fr.Int. - 5 years Improved by thoracoplasty

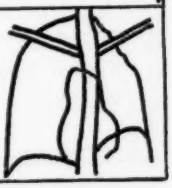


PLATE 2

15

L.W. - F, age 39 (1932) S.C.I

Cause - Chr.Fib.+Phrenic Symptoms - Gradual

Fr.Int.- 7 Partial relief sedatives Otherwise unchanged

16

F.C. - M, age 37 (1932) S.C.I.+Arr.+Decomp.

Cause-Fibrosis-Atelectasis Symptoms-Sudden, 5 weeks

Fr.Int. - 7 Died: Cardiac failure 8 days later

17

R.D. - M, age 49 (1932) S.C.I.

Cause - Effusion Symptoms - Few weeks

Fr.Int. - 12 years Improved by sedation

18

M.R. - F, age 41 (1933) S.C.I.

Cause - Chr.Fib.+Eff. Symptoms - Gradual

Fr.Int. - ? Died: TB, 7 years later

19

G.S. - F, age 28 (1933) S.C.I.

Cause - Chr.Fib. Symptoms - 10 months

Fr.Int. - 0 Died: Non-cong. failure, 3 weeks later

20

C.H. - F, age 52 (1933) S.C.I.+Arr.

Cause - Chr.Fib. Symptoms - 3 years

Fr.Int. - 12 years Improved by sedation

21

A.D. - F, age 47 (1933) S.C.I.

Cause - Chr.Fib.+Pnx. Symptoms - 2 years

Fr.Int. - 6 years Improved on exercise

PLATE 3

22

A.W. - M, age 61 (1933) S.C.I.+Arr.

Cause - Chr.Fib. Symptoms - Gradual

Fr.Int. - ? Improved by sedation: Otherwise same

23

E.F. - F, age 29 (1934) S.C.I.

Cause - Chr.Fib.+Cavity Symptoms - Gradual

Fr.Int. - ? Died: TB, 1 year later

24

M.DeR.-M, age 31 (1935) S.C.I.

Cause-Chr.Fib.+Kyphosis Symptoms - Few months

Fr.Int. - Several years Died: 10 days, cardiac failure without cong

25 F.M. - F, age 44 (1935) S.C.I.

Cause - Chr.Fib.+Pnx.+Effusion

Fr.Int. - 0 Symptoms - 2 years

EKG-1940 normal Seen pr.op. Improved by thoracoplasty

(See Text)

26

G.D. - M, age 37 (1935) S.C.I.+Arr.

Cause - Chr.Fib.+Eff. Symptoms - Gradual

Fr.Int. - ? Died: 1 year later, prog TB lung abscess

Seen pr. op.

27

A.B. - M, age 38 (1935) Ang.

Cause - Pnx. Symptoms - 1 year

Fr.Int. - 5 years EKG - 1935, 1940 normal

Unchanged

28

J.H. - M, age 40 (1935) S.C.I.

Cause - Chr.Fib. Symptoms - Gradual

Fr.Int. - ? Status unknown

PLATE 4

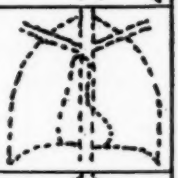
29	E.D. - M, age 30 (1935) Cause - Pnx. Fr.Int. - 3 years ?	S.C.I. Symptoms - Gradual Died:TB 2 years later	
30	A.W. - F, age 52 (1936) Cause - Chr.Fib.+ Atelectasis (bronchial stenosis) Fr.Int. - ?	S.C.I. Symptoms - Gradual Died: Rapid non-congestive failure	
31	J.G. - F, age 28 (1936) Cause - Pnx. Fr.Int. - 0	Ang. Symptoms - Immediate EKG - normal Improved by time, subject to recurrence	
32	W.N. - M, age 42 (1937) Cause - Pnx.+Eff. Fr.Int. - 17 years (See Text)	Ang. Symptoms - Sudden EKG-1937, 1940 normal Status remains same	
33	E.C. - F, age 45 (1937) Cause - Chr.Fib. Fr.Int. - ?	S.C.I.+Arr.+Decomp. Symptoms - Gradual Died: Two days later, congestive failure	
34	W.A.M.-M, age 56 (1938) Cause - Chr.Fib. Fr.Int. - 0	S.C.I.+Arr. Symptoms - Gradual Slight improvement on sedation and exercise	
35	E.E.P.-M, age 62 (1938) Cause - Chr.Fib. Fr.Int. - 27 years	Ang. Symptoms - Sudden, 6 mo. EKG - normal Improved on sedation	

PLATE 5

36
G.F.C.-M, age 42 (1940) Ang.

Cause - Chr.Fib.+Phrenic Symptoms - Gradual

Fr.Int. - ? EKG - Lt. axis dev.(-10°)
Condition unchanged

37
B.B. - M, age 52 (1940) S.C.I.+Arr.

Cause - Chr.Fib. Symptoms - 5 years

Fr.Int. - 0 EKG - Sinus tachy. (124)
Condition unchanged

38 A.R. - F., age 33 (1941) S.C.I.

Cause - Chr.Fib.+Pnx. Symptoms - 2 years

Fr.Int. - 4 years EKG-Rt. axis dev.(-139°)

Died: 2 days later, acute cardiac failure without congestion.

The following abbreviations apply throughout the tabulation:

"S.C.I." - Symptomatic Cardiac Insufficiency
"Arr." - Arrhythmia
"Ang." - Anginoid symptoms
"Chr.Fib."- Chronic Fibrosis
"Pnx." - Pneumothorax
"Eff." - Pleural Effusion
"Emp." - Empyema
"Fr.Int."- Free Interval

Other abbreviations are self-explanatory.

PLATE 6

viously. Dyspnoea, palpitation and tachycardia began at that time and had gradually grown worse. Aside from the marked displacement of the entire mediastinum to the left so that the cardiac apex presented at the anterior axillary line, and a resting pulse of 112 per minute, no cardiovascular abnormality could be demonstrated. After thoracoplasty the symptomatic insufficiency was ameliorated and continues so at the end of five years. The electrocardiogram taken in 1940 is not remarkable.

Case 13: V. H., male. *Symptomatic cardiac insufficiency with arrhythmia:* This thirty-six year old man was seen first in 1932, complaining of dyspnoea, palpitation, tachycardia and irregular heart action. The symptoms appeared with the development of acquired dextrocardia following empyema, complicating pneumothorax in 1924. At first he suffered attacks of paroxysmal tachycardia, which were later supplanted by persistent extrasystoles. The arrhythmia was more troublesome when at rest. In 1937, five years later, he developed episodes of paroxysmal auricular fibrillation, which gradually became less frequent and less severe after about a year. In 1940 he was still the subject of constant dyspnoea, palpitation and "skipping." The extrasystoles are partially controlled by small doses of phenobarbital. His pulmonary disease has been apparently arrested for several years, but he is now semi-invalided on account of his symptomatic cardiac insufficiency. The dextrocardia is marked, the apex lying behind the sternum. The electrocardiogram (1940) shows nothing remarkable except a prolonged A-V conduction time, the P-R interval being .22 seconds.

Case 32: W. N., male. *Anginoid:* This forty-two old male secretary was seen first in 1937, sixteen years after his pulmonary disease had become arrested. Pneumothorax therapy had been discontinued after pleural effusion, which left him with a moderate displacement of the entire mediastinum to the right. The symptoms consisted chiefly of pain originating in the right second interspace, radiating across the chest and down both arms. The pain might follow exercise or interrupt sleep. It was not relieved by vasodilators. Physical signs were absent, except for distortion, and electrocardiograms were normal in 1937 and 1940. Dr. Paul D. White substantiated the author's impression that the symptoms were not of coronary origin.

Case 7: E. M., female. *Symptomatic cardiac insufficiency with pain, without arrhythmia:* This thirty-four year old registered nurse was seen first in 1931. She had had a successful therapeutic pneumothorax from 1919 to 1922, and had been at work as a nurse for the eight years since 1923. She complained of tachycardia, palpitation, oppression in chest, faint attacks, precordial pain and ease of fatigue. She was barely able to continue her duties by resting all hours when off work. There was marked displacement of the mediastinal structures to the left due to the incompletely expansible left lung. The resting pulse rate was 120 per minute. A questionable history of previous thyroid overactivity suggested possible hyperthyroidism. The basal metabolic rate was −6 per cent. She returned to her home, where her physician reported that her tuberculosis later became reactivated and that she died of rapidly progressive, cavitating tuberculosis in 1939.

Case 2: A. B., female. *Symptomatic cardiac insufficiency with pain and arrhythmia:* This patient has been observed at intervals since 1929, when she was first seen at the age of forty-five, complaining of "jumping heart," breathlessness, day and night. She had had chronic fibrocavernous tuberculosis of the left upper lobe for many years, with a resulting distortion of the superior mediastinum far to the left. The dyspnoea had developed gradually over many years but the arrhythmia had existed only a few weeks. The resting pulse rate was 104 and there were many ventricular extrasystoles. She improved some-

what on mild sedation. In 1930 she developed precordial pain, radiating into left arm and shoulder, unrelated to exercise or emotion, but provoked by position, chiefly raising the arm. Pain was not relieved by vasodilators and might be continuous for many hours. In the subsequent years the pain and arrhythmias have recurred at varying intervals but the dyspnoea, orthopnoea and tachycardia have persisted. There has never been any objective evidence of congestive failure but she remains definitely handicapped by her cardiac symptoms. The blood pressure was still within normal limits in 1940. Electrocardiograms in 1929, 1932, 1938 and 1940 were all normal.

DISCUSSION

Evidence in favor of the theory: Admittedly there is no actual proof that distortion of the mediastinum and its contents may cause cardiac symptoms. Yet the arm of coincidence does not seem long enough to account for the fact that 38 such cases should pass through the hands of a single observer. The inference as to a causal relationship seems inescapable. Similar and supporting observations have been made by Hawes (40), Houcke and Salembier (43), d'Hour (44), Huriez (45), Kahn (48), Koester (50), Rist and Ameuille (68), Rubin (70), Sega (74), Swoboda (78), Tildon (81) and Ziskin (86), in addition to those cited elsewhere in this article.

Even more direct evidence is offered by the improvement seen in certain cases after thoracoplasty. Instances were observed by Smith (77), Hedblom (41), and Beck (9). Three of the author's cases illustrated the same point. In one of these, case 6, there was a delay of several months between the first and second stages of the thoracoplasty. The first stage was followed by decreased displacement and prompt improvement of the cardiac symptoms. The pulmonary disease was not controlled until after further surgery, refuting the suggestion that thoracoplasty relieves the heart symptoms by reducing the toxaemia alone.

Harter, Overholt and Perkin (39) record 2 cases in their series on lung volume studies, before and after thoracoplasty, in whom dyspnoea was relieved by the operation in spite of a decrease in vital capacity. Other cardiovascular symptoms were not reported. One was shown by roentgenograms to present a marked superior mediastinal displacement to the left. The mediastinal position of the other was not recorded.

Theories as to cause of symptoms: The search for a specific explanation of the mechanism producing these symptoms leads at once into the realm of speculation. Various theories have been advanced involving separate features of the distortion and quite different deranged structures have been indicated as the seat of the disturbances.

Beck (9) made some remarkable observations while directly manipulating the exposed heart. Direct traction in the long axis of the heart and simple lateral displacement produced no effect, but rotation of the organ on its vertical axis or angulation on the axis of its anchorage at once altered both rate and rhythm. These experiments would suggest that the presence or absence of rotation in addition to lateral displacement might explain why some patients with displacement experience tachycardia and arrhythmia, while others do not. Raimondi, Capdehourat and Mazzei (67) report a case of therapeutic pneumothorax in whom

arrhythmia developed after refills and disappeared upon discontinuing the pneumothorax, and the writer (18) reports one case in whom refills were followed by paroxysmal auricular fibrillation.

Beattie, Brow and Long (8) among others proved experimentally that stimulation of the sympathetics caused tachycardia and extrasystoles. It seems self-evident that any major lateral deformity must alter the relations and tension of the extrinsic cardiac nerve plexuses and set the stage for easy overstimulation, either by direct action or by lowering the nerve threshold. Marked displacements of the superior mediastinum should be particularly productive of this type of circumstance. In substantiation of this idea of sympathetic influence is the author's experience that these extrasystolic arrhythmias are partially relieved by raising the nerve threshold with small doses of mild sedatives, phenobarbital or bromides, either alone or in combination.

There is concrete evidence that nerves may be severely stretched by shifting viscera, as shown by one case in this series. A man of thirty-nine, case 16, was seen only *in extremis*. He had a violent antipathy toward physicians and had insisted on going unattended for many months, until the development of aphonia led him to call a laryngologist who discovered a paralyzed left vocal cord and insisted that the man have other medical attention because of his desperate condition. He had suffered a marked displacement to the left due to fibrosis and probably atelectasis of the entire left lung, dragging the arch of the aorta far to the left and downward, inevitably stretching the left recurrent laryngeal nerve. It is possible that the nerve may also have been involved in fibrosis but the opportunity to settle this at autopsy was denied. He had had rapidly increasing cardiac symptoms for five weeks, starting as symptomatic insufficiency with extrasystoles, but congestive failure had entered the picture when seen. He refused all attention other than symptomatic treatment and would not even allow bedside X-ray examination. There was no evidence, by history or physical examination, of preëxisting cardiovascular disease.

Farris (28) reported 2 of his atelectasis patients with extreme displacement to the left in whom extreme hoarseness accompanied the cardiac symptoms. Both were relieved promptly when the mediastinum was returned to its normal position. He attributes the hoarseness to tension on the recurrent laryngeal nerve. Swynghedauw (79) lists dysphonia—*la voix bitonale*—as one of the symptoms of severe displacement, and Leonard (53) also has noted paralysis of the vocal cord.

Other important structures participating in these derangements are the great vessels. The aorta, pulmonary arteries and the veins of both the systemic and pulmonary circulations are obviously subject to severe torsion and angulations. The venae cavae theoretically should suffer more than the arteries, their thin walls yielding to outside pressures and inevitably becoming stretched and angulated with any marked lateral displacement of the heart itself. The inferior vena cava, with its fixed diaphragmatic portal, has been seen to make a 45 degree angle with the horizontal plane at the diaphragm. Such an angulation, in the course of any great vessel, mechanically decreases the lumen at the point of

angulation and would affect the free flow of blood, even though the constriction should never become severe enough to cause distal oedema. Descomps (26) attributes the circulatory disturbances to deformity of the pulmonary artery.

The most logical theory, from the evidence at hand, as to the specific aetiology of the cardiac symptoms occurring in cases of mediastinal distortion is that they are the result of a combination of the factors concomitant to the distortion. This hypothesis considers that changes in the position of the heart with reference to its axes, torsion and angulation of the great vessels, and disturbances in the relations of the sympathetic plexuses supplying the heart, may all participate in causing symptoms. Similar views have been expressed by Swynghedauw (79), Sayagués (72), de Véricourt (85) and Lardanchet (52).

Consideration must be given to the respiratory factor in the production of symptoms, although the suggestion, frequently advanced, that all may be on a purely respiratory basis is not tenable. Certain authors, notably Biasini (11), Génévrier and Descomps (33) and Pfeil (64) make much of the handicap imposed upon the right heart by the pathological changes in the collapsed or fibrotic lung. The reduction of the capillary bed by fibrosis and the associated endarteritis all, presumably, increase the arterial tension in the lesser circulation to the ultimate detriment of the myocardium. Doubtless there is a respiratory factor in many cases. No one would deny that extensive progressive intrapulmonary fibrosis will eventually reach the stage causing respiratory insufficiency and *cor pulmonale*. The same holds for true pulmonary emphysema, and when the latter is secondary to the former, and concomitant, right heart failure is a common outcome. Even lesser degrees of these pulmonary changes may have some influence. Anoxaemia, of whatever origin, should be credited with its due part in the production of dyspnoea, and its direct unfavorable effect on the myocardium must be recognized.

Likewise, there is the mechanical respiratory difficulty occasioned by fixed chest, whether fixed in contraction due to intrapulmonary fibrosis or adhesive pleuritis, or fixed in hyperexpansion by an extreme emphysema. Lardanchet (52), Sayagués (72) and Cavarozzi (19) emphasize the influence of the loss of normal pulmonary expansibility, whether through fibrosis and contraction of one lung or due to fixation by unilateral pleural symphysis, upon the systole of the heart itself. They maintain that this intrathoracic disequilibrium distinctly interferes with the normal cardiac contractions. The fall of systemic blood pressure during inspiration is offered as proof by Sayagués (72). Toxaemia undoubtedly contributed to the symptoms of those patients who were acutely ill from their chronic infection but could have had no direct influence upon those cases with long healed and quiescent pulmonary disease. Mahon and Grow (55) list mediastinal distortion as one cause of pulmonary hypertension and report cases dying of right heart failure with arrested fibrotic lesions.

There is a striking similarity in the cardiac failure displayed by some of these cases and that recorded for severe kyphoscoliosis and funnel chest by such authors as Boas (13), Coombs (24), Schaefer (73), Smith (76) and Traube (82). The deformity of the bony thorax imposes a derangement of the thoracic viscera

comparable in every way to that resulting from pleuro-pulmonary disease, and with parallel effects on the circulatory system. One case, number 24, suffered both chronic fibrosing pulmonary tuberculosis and marked kyphoscoliosis. He succumbed to rapid cardiac failure.

Electrocardiographic findings: The electrocardiographic findings on the 12 cases on whom tracings were made were surprisingly normal. The studies of Bosco (14, 15), Pérez de los Reyes (62), Agnoli (1) and Treiger and Lundy (83) would lead to the expectation that there might be axis deviation in proportion to the lateral shift of the heart. Leverton (54), as well as Kountz and his coworkers (51), indicates that rotation is more significant in causing electrocardiographic axis changes, than is displacement. Only 3 of the 12 showed abnormality of this kind (numbers 6, 36 and 38) a proportion in substantial agreement with the results obtained by Hansen and Maly (36, 37), Hansen and King (35), King and Hansen (49), d'Ovidio (59), Simon and Baum (75) and Anderson (4). The only other significant abnormality occurred in case 13, a prolongation of the P-R interval to .22 seconds.

Incidence of symptoms in cases of mediastinal deformity: Statistics as to the percentage of persons suffering these mediastinal distortions who develop cardiac symptoms would be enlightening but, unfortunately, are not available. The high incidence of some degree of displacement among the chronic tuberculous has long been recognized. Clark, Hadley and Chaplin (21) pointed this out in 1894, as did Brown (16) in 1908, Francine (32) in 1910 and Fishberg (30) in 1914. Joannides' (47) more recent studies emphasize the same fact.

Trémolières and Ménillet (84) go so far as to state that functional cardiac symptoms rarely, if ever, occur in acquired dextrocardias, but they stand almost alone in this conclusion.

The author has been unusually fortunate in that Saranac Lake affords a unique field for this kind of clinical material. Many former patients make the community their permanent home after rehabilitation; many true chronics unsuitable for surgery, or refusing it, make this their semi-permanent residence; a fair number of permanently semi-invalided individuals divide their years between the other resort communities and Saranac Lake; and lastly, a considerable number come here specifically to receive thoracic surgery. It is in just such groups that this combination of clinical features would be expected to arise. The local physicians have recognized the writer's interest by making these cases available for observation. It is obvious that this experience can give no fair idea of the incidence of cardiac symptoms among patients with mediastinal distortion because only those cases with cardiac problems were referred.

Prognosis: From this series the prognosis in this condition would seem to be as difficult as the prediction of its occurrence. Information, of from a few months to eleven years later, is available (see Compendium of Cases) on 37 of the 38 cases. Of these, 19 were living in January, 1941 and 18 were dead. Among the living, 3 were improved by thoracoplasty; 4 were improved by graduated exercise (one completely); 4 have been controlled by mild sedation with avoidance of stimulation; 7 have remained practically unchanged, although temporarily

benefited by sedation; and one has developed paroxysmal auricular fibrillation, in addition to his other symptoms, after five years.

Of the 18 dead, one died of a wholly unrelated cause (intestinal haemorrhage); 8 met typically toxaemic or asthenic deaths from progressive pulmonary tuberculosis; one succumbed to progressive tuberculosis but with a cardiorespiratory type of death; 4 died of congestive heart failure; and 4 had cardiac deaths without congestive failure. In several of these last two groups the heart symptoms progressed in the face of a stationary pulmonary condition and the final failure of the heart was precipitous. The cases with congestive failure proceeded to a fatal outcome rapidly and uninterruptedly once oedema made its appearance. This can mean only that rapid and complete insufficiency of the right myocardium had ensued, but these cases differ from the usually observed patients with right heart failure in the speed with which death followed the first visible results of peripheral congestion, a fact also noted by Nemet and Rosenblatt (58). In the deaths without congestive failure the picture was that of a climax of dyspnoea, orthopnoea, cyanosis, rapid and failing pulse, suggesting the concentric myocardial collapse seen in acute dilatation. Acute pulmonary oedema, such as that seen in acute left heart failure, was not observed. Such pulmonary oedema as did occur was the natural result of the general terminal circulatory failure rather than the preterminal precipitating event.

This wide variation in clinical behavior and progression puts any long-range prognosis on dangerous footing. We have seen complete recovery, symptomatic relief, stationary symptomatology for many years and finally true cardiac death, ignoring for the moment those cases dying of obviously and typically tuberculosis progression. Why should an occasional one improve, many remain much the same and several others eventuate in cardiac death? Several trains of speculative thought arise. Perhaps some may harbor unsuspected inherent or acquired myocardial weakness which abruptly surrenders to the increased difficulties under which the heart has been working, while in others a sound myocardium carries on much the same year after year in the face of the symptom-producing factors. Perhaps neurogenic symptoms may be well borne while even an originally sound heart muscle may eventually weaken before unrelenting mechanical strain. In this circumstance the heart would be expected to pass through a stage of preliminary hypertrophy before failure occurred, a condition not encountered in this series.

Treatment: Treatment may be discussed under three headings: prevention, nonsurgical and surgical. Needless to say, prevention, when it can be effected, is the most important. In many cases it will be impossible to prevent the distortion by justifiable means, even if the end-result could be clearly anticipated, which it often cannot. In the patients with fibrosis, contraction and cavity, earlier thoracoplasty, as is now generally practiced, will effectively forestall many severe displacements. In the cases receiving pneumothrax therapy, distortion may be unpredictable far enough in advance to permit prevention. Unless the involvement of lung tissue is so extensive, either by infiltration or cavity, that the healed lung must obviously be seriously contracted, it will be difficult to judge

its reëxpansibility until the treatment is being discontinued. Markedly thickened pleura is, of course, a readily recognized and insurmountable obstacle to reëxpansion of the lung. Some phthisiologists advocate temporary phrenic paralysis to cushion against too great displacement when pneumothorax is to be discontinued if the lung is slow to reëxpand. Abrupt cessation of refills would never seem advisable unless the lung periphery were already near the chest wall.

Nonsurgical treatment of the distortion, when well established, avails little, although Clayson (22) reports success in restoring early displacements by systematic deep breathing exercises. Preventive deep breathing was used routinely at the Smithfield Sanatorium with the gratifying result that only 3.5 per cent of their cases showed displaced hearts. It is warned that the deep breathing treatment of displacement is useless after phrenic nerve paralysis.

Symptomatic treatment is often necessary. None has been found wholly satisfactory but considerable relief may be afforded. As previously mentioned, the palpitation, due to tachycardia and extrasystoles, can be partially controlled by giving small doses of mild sedatives.

Surgical measures for the treatment of the distortions should be considered when the symptoms are severe. Davies (25), Besta (10), Günther (34) and Harper (38) report successful results with phrenic nerve interruption. In their cases the rise of the hemidiaphragm was accompanied by a demonstrable decrease in the displacement and relief of symptoms. Alexander (2) and Pfeiffer (63) also comment on the lateral shift of the heart following phrenic interruption. The results from thoracoplasty have already been noted and Swynghedauw (79) recommends it. It is doubtful, however, whether many patients would accept thoracoplasty for relief of the cardiac symptoms unless it were indicated, at the same time, for the tuberculous process itself. Perhaps we may, some day, include this syndrome as an indication for thoracoplasty, even in the presence of healed pulmonary disease. From the evidence at hand many cases would seem, logically, to benefit from such surgical procedure.

Further studies indicated: Many questions must be answered and many further critical investigations be made before this can be considered a closed subject.

From the standpoint of prognosis and prevention, we would like to know what proportion of patients with distortion may be expected to develop cardiac symptoms and, if possible, how to predict which patients will be most likely to be afflicted. At present such predictions are not possible and, accordingly, all must be considered potential cardiac sufferers. Studies, such as those of Robb and Steinberg (69), should be useful in evaluating the part played by torsion in the production of arrhythmias or in quantitatively assaying the rôle of angulation of the great vessels. More physiological studies on respiratory and circulatory function are needed. The presence of preclinical anoxia may prove helpful in anticipating the subsequent course of events.

SUMMARY

Clinical observations are reported on 38 persons having distortion of the mediastinal structures due to pulmonary tuberculosis in whom cardiac symptoms

had developed with no demonstrable organic cardiovascular disease. The evidence points strongly to the conclusion that such distortions may be the cause of the cardiac symptoms. This idea is supported by other observers in the literature.

The causes of the deformity, the type of deformity and the varying symptom complexes are discussed.

Theories are advanced as to the mechanism producing symptoms.

Suggestions are offered regarding prevention of the distortion and for the treatment of the cardiac symptoms, as well as for correction of the distortion when symptoms have arisen.

SUMARIO

Comunícanse las observaciones clínicas de 38 personas con distorsión de los tejidos mediastínicos, ocasionada por tuberculosis pulmonar, y en que los síntomas cardíacos no se asociaron con afección cardiovascular orgánica demostrable. Los hallazgos apoyan poderosamente la deducción de que dichas distorsiones pueden ocasionar los síntomas cardíacos. Otros observadores y la literatura apoyan esta hipótesis.

Discútense las causas y tipo de la deformidad, y los varios complejos sintomáticos.

Propónense varias teorías en cuanto al mecanismo causante de los síntomas.

Ofrécense indicaciones para la prevención de la distorsión y para el tratamiento de los síntomas cardíacos, así como para la corrección de la distorsión cuando ya se han presentado los síntomas.

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THE HEART IN PULMONARY TUBERCULOSIS[1]

A Clinico-Pathological Study of 100 Autopsied Patients

J. EUGENE ROBERTS AND JAMES R. LISA

This communication is the report of a study of the cardiac lesions found among 100 cases of pulmonary tuberculosis on whom necropsies were performed at City Hospital, Welfare Island, New York. Myocardial lesions of various kinds were present in 69 instances. An attempt will be made to evaluate their rôle in the clinical manifestations of cardiac dysfunction, occurring in the presence of pulmonary tuberculosis. The findings by other methods of clinical study will be discussed.

The 100 cases were chosen on the basis of the presence of extensive active pulmonary tuberculosis: in 35, the lesions were confined to the lungs; in 65, other organs were also involved.

The age range was wide. The youngest individual was a Negro baby, eleven months old; the oldest were 2 white men of 83.

Decade	*Number*
0–10 years	4
11–20 years	5
21–30 years	18
31–40 years	17
41–50 years	13
51–60 years	16
61–70 years	19
71–80 years	6
81–90 years	2
Total	100

There were 67 males and 33 females. Among the males, 52 were white, 14 black, one Japanese. Among the females, 16 were white and 17 black.

Tuberculous pericarditis was present twice. The pericardium was diffusely adherent without evidence of tuberculosis in 3 cases. There were 3 instances of acute nontuberculous pericarditis. A slight excess of clear fluid was frequently present.

The weight of the heart was recorded in 92 cases.

Heart Weights

Weight in grams	*Number of cases*
100–200	5
201–300	36
301–400	34
401–500	8
501–600	6

[1] From the Pathological Laboratory, City Hospital, Welfare Island, Department of Hospitals, New York, New York.

Weight in grams	*Number of cases*
601–700	1
701–800	0
801–900	2
Not weighed	8
Total	100

The average for all cases was 304 g. Among the adult males it was 331 g. and among the adult females 280 g. The conception that the tuberculous patient usually has a small heart has led to considerable controversy. Strauss (1a) recognized this difference of opinion but stated that a small heart, at least to the naked eye, is common in pulmonary tuberculosis. King and Hansen (2) studied the weights in 100 cases. They found the hearts of males heavier (318 g. *vs.* 294 g.) and of females lighter (220 g. *vs.* 250 g.) than the normal standard weights of Smith. However, they concluded that the hearts in tuberculous patients were smaller than in the nontuberculous, if all factors were taken into consideration. Norris and Landis (3a) quoted White's belief, based on a study of 197 necropsies, that both males and females had practically normal average weight of the heart. In the present series, although 19 hearts weighed less than 250 g., the average of either sex was slightly above Smith's standards. Our findings are not in conformity with the traditional conception that the tuberculous individual characteristically has a small heart.

Increased thickness of the ventricular walls suggestive of cardiac hypertrophy was found in 14 instances. Four were predominantly left ventricular, 4 predominantly right and 6 were of both ventricles. A marked discrepancy was noted, however, between the diagnosis made on the gross appearance and that made upon histological examination. The latter method revealed 38 cases with left ventricle hypertrophy, 2 with both left and right ventricular hypertrophy and only one of isolated right ventricle hypertrophy. The frequency of right heart hypertrophy in pulmonary tuberculosis has caused widely diverse opinions. Fishberg (4a) stated that it is not uncommon in fibroid phthisis. He believed the question was solved by studies in which the individual chambers of the heart were weighed separately. Strauss agreed with Fishberg that right ventricular hypertrophy was apt to be found. Nemet and Rosenblatt (5), in a study of 71 cases, found right ventricular hypertrophy in 46.5 per cent and isolated right sided hypertrophy in 33.8 per cent. Their figures were based largely on gross evidence, but among the instances of isolated right sided cases, 3 were so judged on the histological appearance of the muscle. Among 330 cases studied by Ackerman and Kasugi (6) there were 53 instances, or 16 per cent, of chronic *cor pulmonale*. They used as their criteria a thickness of the right ventricle of 5 mm. or more. Using similar criteria, Griggs *et al.* (7) found only 6, 3.7 per cent, with right ventricular hypertrophy among 1,480 cases. No hypertrophy of any type could be demonstrated in 90.8 per cent. They stressed the finding that, among all types of chronic pulmonary diseases, only chronic bronchitis had a lower incidence of right ventricular hypertrophy. Our findings are

in much closer agreement with those of Griggs than with those of other investigators. We believe that the disagreements are due largely to the criteria based on macroscopical examination. We also believe that the histological examination gives a more reliable and more correct conception of cardiac hypertrophy than the thickness of the wall. Based on histological criteria of myocardial hypertrophy, there were only 2 instances of combined left and right ventricular hypertrophy and only one of isolated right ventricular hypertrophy in this series.

The gross appearance of the myocardium was frequently abnormal, being pale, mottled, flabby or discolored in 44. Fine or coarse scarring was found in 6. Healed infarctions were present in 3 and acute massive infarction in one. In 56 hearts there were either minimal or no changes.

Microscopical studies revealed myocardial lesions in 69 hearts. There was tuberculous myocarditis in 10, acute rheumatic myocarditis in one, Aschoff-like lesions in 9, acute interstitial myocarditis in 50 and acute miliary infarctions in 11. In 13 instances, combinations of the lesions were present. In 6 cases each, acute interstitial myocarditis occurred with miliary infarctions or with Aschoff-like lesions. One case had tuberculous myocarditis and miliary infarctions.

Tuberculous myocarditis was a manifestation of acute generalized miliary spread in 8 instances. In 2, it was associated with tuberculosis limited to the lungs. In 6 cases it was limited to the left ventricle. In one, it was part and parcel of an early pericarditis and only the superficial myocardium was involved and was discovered only microscopically. Three cases had right ventricular localization, one epicardial, two endocardial and subendocardial.

One case was found in the second decade, 3 in the fourth, 2 each in the sixth, seventh and eighth. Horn and Saphir (8) concluded from their own observations and from a survey of the literature that tuberculous myocarditis was more prone to develop in children than in adults. Auerbach and Guggenheim (9), from a review of 10,165 autopsies on tuberculous patients of all ages reported in medical literature, found that myocardial involvement occurred in only 0.28 per cent, but among 973 children the incidence was 3.9 per cent. In our series, there were 6 patients below the age of seventeen; tuberculous myocarditis occurred in one. Among the adults, 92 in number, tuberculosis of the heart occurred in 7.

Acute interstitial myocarditis was present in 50 hearts to a moderate or extensive degree. In 21 others, foci of similar nature were found but were considered of no particular significance because of their sparce occurrence. The presence of interstitial myocarditis bore no demonstrable relation to heart weights, but did appear to have some relationship to nontuberculous infections. This point will be discussed later. Wuhrmann (10) observed the same lesion. Although when first observed he believed the lesion nonspecific, he concluded that it might well be tuberculous in nature, due either to the toxins of tuberculosis or to a haematogenous spread of the organisms. He postulated a low-grade tuberculous infection of the myocardium causing a diffuse exudate and not tubercle formation. He was impressed by the frequent time relation between a clinical

increase in the tempo of the pulmonary tuberculosis and the presence of the interstitial myocarditis. We have observed a similar interstitial myocarditis in many other conditions of nontuberculous nature and are inclined to receive Wuhrmann's hypothesis with reservation.

Miliary infarctions were present in 11 hearts. They were scanty in 5, moderate in number in 2 and abundant in 4. As noted above, they frequently were associated with other lesions of the myocardium. They also were more frequent in the hypertrophied hearts. In 41 hearts weighing 300 g. or less, they occurred twice; in 34 hearts weighing 301 to 400 g., three times; and among 17 over 400 g., five times. They also tended to appear among the older individuals, the majority above the sixth decade.

There was only one case of active rheumatic heart disease. It was an acute myocarditis without valvular involvement and was discovered only by microscopy.

Granulomatous lesions closely resembling the Aschoff body were present in 9 hearts. They were perivascular in site and fusiform to triangular in shape. They consisted of Aschoff or Anitoschkow cells, a few lymphocytes and rarely some polymorphonuclear cells. There was some fibrinoid degeneration of the collagenous fibres but it was marked only in one instance. In 5 cases the lesion closely resembled the Aschoff body. In 4 the resemblance was less close; the Aschoff cell had a smaller nucleus and less abundant cytoplasm. In 4 they were localized deep in the left ventricular muscle; in 2, deep in the right ventricle and in the other 3, in the subendocardial zone, once on the right and twice on the left. They were not found in the auricles. This lesion has been observed in various conditions and its aetiology remains obscure. Saphir (11) found it in 24 of 240 cases of myocarditis of various aetiology. Schmorl (12), Fahr (13) and Kirch (14) studied it in scarlet fever. Ehrlich and Lapan (15) saw it in sepsis, meningococcal bacteraemia, scarlet fever, periarteritis nodosa and subacute endocarditis. Among 120 patients dying of acute infectious diseases, such as scarlet fever, typhoid, pneumonia, endocarditis, sepsis and pharyngitis, Yamada (16) found the lesion in 13 hearts. He also found it among cases of tuberculosis. He stated that the lesion in the nontuberculous was more exudative and more closely similar to the Aschoff body than that occurring in tuberculosis. Masugi (17) observed it in 35 of 215 cases of tuberculosis. Takedo and Simpo (18), in 350 cases dying from tuberculosis, saw it in 39. Wuhrmann was unable to find the lesion in tuberculosis. Masugi was of the opinion, based on a study of the lesion seen in tuberculous cases and in rheumatic fever, that rheumatic fever might be tuberculous in nature. Yamada and Wuhrmann disagreed with this idea. Wuhrmann believed that Masugi's cases were combined rheumatic fever and tuberculosis.

The coronary arteries were moderately or severely sclerotic in 11, had slight atheroma in 20 and were normal in 69. One heart had an old canalized thrombus. The condition of the coronary arteries could be related only to one type of acute myocardial lesion. Miliary infarctions were present in 6 of the 11 hearts having moderate or severe sclerosis, once in the 20 with mild lesions and four

times with normal vessels. The occurrence of the lesion in 54 per cent of the cases with severe arteriosclerosis, as contrasted with 5 per cent in each of the other two groups, is in agreement with similar observations reported from this institution (19, 20).

Healed rheumatic mitral valvulitis was present in 5 hearts. Twenty showed definite sclerotic changes of the aortic and mitral valves. There were 2 cases each of acute valvular endocarditis and syphilitic aortic valvulitis. The mural endocardium was greatly thickened in 4. Mural thrombi were present in 9; one was septic due to *B. coli* infection, one was secondary to a tuberculous myocarditis and mural endocarditis.

Extracardiac nontuberculous infections were present in 86 cases. In 14 there was neither gross nor microscopical evidence of such a complication. In each of these two groups, acute interstitial myocarditis occurred in 50 per cent. Upon dividing the nontuberculous infections according to site, one with pulmonary, one with extrapulmonary and one with combined pulmonary and extrapulmonary tuberculosis, the interstitial myocarditis was seen to occur in 52 per cent of the first group, 26 per cent of the second and 58 per cent of the third. Although the series is not large enough to justify a definitive conclusion, a relationship between pulmonary infection and acute interstitial myocarditis seems to exist. Tuberculous myocarditis and the Aschoff-like lesion occurred in about equal frequency in the infected and noninfected groups.

The clinical records were reviewed to determine the presence of symptoms and signs indicative of cardiac disease and failure. This was frequently rendered difficult due to inadequacy of data pertaining to the cardiovascular system. Dyspnoea, precordial pain, chest pain and cyanosis could be accepted only if far out of proportion to the existing lung involvement. Dependent oedema, ascites, hepatic enlargement and basal lung râles all had to be judged with caution. However, 75 cases could be accepted as free of cardiac symptoms, 5 had questionable ones, and 20 persented definite findings of failure coexisting with active tuberculosis. The myocardial lesions present in these 20 cases were tuberculous myocarditis 5, interstitial myocarditis 10, miliary infarction 3 and Aschoff-like lesions 2.

An apical systolic murmur was heard in 9. One had a sclerotic mitral valve, 3 healed rheumatic mitral stenosis, 3 mural thrombi, 2 had no gross lesions. One had a combined systolic and presystolic murmur. The mitral valve had a sclerotic nonrheumatic lesion. One case had an apical presystolic murmur without a demonstrable valvular lesion. The one case with an aortic systolic murmur had a syphilitic aortic valvulitis. Combined aortic and mitral systolic murmurs were present in 4 cases; 2 had sclerosis of both valves, one had syphilis of the aortic valve and in one no lesions were present. The only case with a systolic pulmonic murmur had sclerosis of mitral and aortic valves.

It is generally accepted that valvular disease is uncommon and that functional murmurs are frequent in tuberculosis. According to Norris and Landis (3b) cardiorespiratory murmurs are common and usually associated with rapid heart action. Strauss (1b) considered systolic murmurs uncommon and occur-

ring either at apex or base. He postulated the cause as myocardial degeneration with dilatation of the rings, pleuro-pericardial lesions or pressure or pulling on the great veins. The findings in the present series suggest that a cardiac murmur should not be called functional too hastily and the cardiovascular system should be carefully explored.

The relative intensity of the second aortic and pulmonic sounds is noted in 27 cases. The aortic sound predominated in 11, the pulmonic in 13, and they were of equal value in 3. The question of accentuation of these two sounds is of special interest. In the study of 20 cases of tuberculosis in whom the heart was centrally situated and the second pulmonic sound accentuated, Kennedy (21) noted that 13, or 60 per cent, died. Of 18 cases with the heart in a similar position but with an accentuated second aortic sound, 7, or 39 per cent, died. He believed it was evidence of right heart strain and carried a poor prognosis. He also found the accentuation of the aortic second sound was rare in tuberculosis unless it was associated with systemic hypertension, calcification of the aortic valve or left ventricular hypertrophy. In the present series, the findings could not be compared with those of Kennedy because of insufficient roentgenological data. No opinion can be expressed in reference to Kennedy's conclusions.

The occurrence of a pulse-temperature disproportion was studied. It is usually believed that tachycardia is commonly associated with active tuberculosis. Strauss stated that the causes are the action of the tuberculous toxaemia, pressure upon the nerves, diminution of the respiratory area with secondary acceleration, vagal neuritis, heart disease or cachexia. Boas (22) was of the opinion that it was functional. Lisa, Solomon and Eckstein (23) believed it was an indication of acute myocardial damage in the majority of instances. In the present series, 23 cases had a mild disproportion (10 to 20 pulse beats above the expected pulse rate for the temperature level), 16 had a moderate disproportion (20 to 30 beats) and 40 had a marked disproportion (over 30 beats). Fifty-four, or 81 per cent, of 66 cases with myocardial lesions had a disproportionately high pulse rate. Of 30 cases without lesions, 23, or 70 per cent, had the same type pulse-temperature relation. Four cases were eliminated from consideration because of severe pulmonary haemorrhage. The difference in incidence was not striking in the total series. However, when analyzed according to the distinctive pathological lesions, it was found that every case of interstitial myocarditis had a severe discrepancy between pulse and temperature, as did the case of acute rheumatic myocarditis. Among the other lesions, only a moderate or severe disproportion seemed of significance. The number of cases however was too small to be certain of conclusions.

Roentgenological studies of the heart were made in 18 cases. The heart was found normal in size in 9, small in 4, enlarged to the left in one and enlarged to the right in 4. Porter and Gordon (24) employed teleo-roentgenograms in the study of 400 patients, comparing the measured transverse diameter of the heart with the predicted transverse diameter. Of these cases, 50.5 per cent had a measured diameter greater than the predicted, 41.5 per cent had a lesser and in 8 per cent they were equal. They concluded that there was no significant difference between the tuberculous individual and the general average. Schmidt

(25) studied 750 consecutive cases and found small hearts in 19.5 per cent. The lack of definite variation in average size is in agreement with the average weights discussed in a previous paragraph.

Blood pressure readings were recorded in 75 cases. They were slightly elevated in 5 (systolic 140 to 150, diastolic 90 to 100), moderately elevated in 3 (systolic 150 to 180, diastolic 100 to 120) and markedly elevated in one (systolic 210, diastolic 130). It is usually held that active tuberculosis and hypertension are rarely associated. Strauss (1d) cautioned against diagnosing tuberculosis in the presence of hypertension. Bunte (26) found only one instance among 504 active tuberculosis cases. Ayman (27) failed to find any among 240. He postulated a tuberculous toxaemia with hypotensive activity able to reduce a preëxisting hypertension. If both tension and tuberculosis were present, he stated that the tuberculosis was apt to be mild and fibrotic. However, the incidence of positive tuberculin reactions was the same in hypertensive patients (90 per cent) and nonhypertensive tuberculous patients (91 per cent). Grant (28) found 5, or 3 per cent, of 140 tuberculous patients to have systolic readings above 150. Masten (29), in a study of 230 cases, found 6.5 per cent with pressures above normal but only 2.6 per cent with pressure above 150 systolic. The findings in this series are more in conformity with those of the last quoted observers. Nor did our data confirm the statement of Ayman concerning the type of activity of the tuberculous lesion. Of the 8 cases with slightly or moderately elevated pressures, only one had somewhat limited lesions, 3 had miliary tuberculosis, 4 had bilateral lesions with multiple cavitation. The single case with very high pressures had extensive chronic lesions of many organs including the adrenals and vertebrae.

Electrocardiographic tracings were taken in 19 cases. The various changes observed are listed as follows:

Prolonged conduction time	4
Left axis deviation	8
Right axis deviation	4
Chronic auricular fibrillation	1
Premature contractions	
Auricular and ventricular	1
Ventricular	1
QRS wave	
Slurring	6
Low voltage	2
T-wave (low, inverted)	
Broad or slurring	12

Strauss (1e) stated that the electrocardiogram remains usually unchanged in tuberculosis, the most frequent abnormalities being right or left deviation, low voltage and *T*-wave changes. Boas and Mann (30), in 92 cases, found right deviation in 29 per cent, left deviation in 30 per cent and neither in 41 per cent. Simon and Baum (31) found 10 per cent right preponderance among 250. In 47 cases not subjected to collapse therapy, Gosse and Wingfield (32) found an equal distribution between normal and abnormal tracings. Among 24 cases with pneumothorax, an equal per cent (9 per cent) showed right or left

deviation. They concluded that the therapeutic procedure gave no constant or predictable change. In the present series, left deviation occurred in 42 per cent, right deviation in 10 per cent. Seventeen of the 19 cases with tracings had demonstrable myocardial lesions. However, these cases had all presented definite symptoms suggestive of cardiac dysfunction.

Haematological studies were carried out in 29 cases. Nine had erythrocyte counts below three million. Seventy-six had evidence of greater or lesser haemorrhage which may have modified some of the counts.

Erythrocyte sedimentation times were estimated in 37 cases. The rate was below thirty minutes in 20, between thirty and sixty minutes in 13 and above one hour in 4. No relationship could be demonstrated between the rate and the presence of secondary infection or myocardial damage.

SUMMARY AND CONCLUSIONS

The findings in a clinico-pathological study of the heart in 100 cases of active pulmonary tuberculosis are presented. Demonstrable myocardial lesions were present in 69. They consisted of tuberculous myocarditis in 10, acute rheumatic myocarditis in one, Aschoff body-like lesions in 9, acute interstitial myocarditis in 50 and acute miliary infarctions in 11. Combinations of the lesions were found in 13. Healed rheumatic valvulitis was found in 5, sclerotic lesions of the mitral and aortic valves in 20, acute valvular endocarditis in 2 and syphilitic aortic valvulitis in 2. There were 3 instances each of tuberculous, chronic adhesive and acute nontuberculous pericarditis. Tuberculous myocarditis was more frequent in the adults than in children. Nontuberculous pulmonary infections appeared to be a significant factor in the causation of the interstitial myocarditis. Miliary infarctions occurred predominantly in the hypertrophied hearts, in hearts with severe coronary arteriosclerosis and in the later decades of life. The conception of a small heart in tuberculosis was not substantiated. Right ventricular hypertrophy was very uncommon. Mensuration of the ventricular wall appeared to be an unreliable criterion for hypertrophy; the microscopical appearance of the myocardial fibres appeared more accurate. A moderate or severe disproportion between pulse rate and height of temperature was suggestive of myocardial disease. Murmurs due to organic valvular lesions were fairly common. Functional murmurs were uncommon. The conception that hypertension and active tuberculosis are incompatible was not borne out. Electrocardiographic tracings frequently revealed significant observations. While the present series is too small to permit definite conclusions about many controversial points, it is the belief of the authors that more attention paid to the cardiovascular system in the tuberculous individual will result in a more accurate estimation of existing cardiac damage.

SUMARIO Y CONCLUSIONES

Preséntanse los hallazgos de un estudio clínicopatológico del corazón en 100 casos de tuberculosis pulmonar activa, 69 de los cuales revelaban lesiones miocardíacas demostrables: miocarditis tuberculosa en 10, miocarditis reumática

aguda en uno, lesiones parecidas a cuerpos de Aschoff en nueve, miocarditis intersticial aguda en 50, infartos miliares agudos en 11. En 13 observáronse combinaciones de varias lesiones, en 5 descubrióse valvulitis reumática cicatrizada, en 20 lesiones escleróticas de las válvulas mitral y aórtica, en 2 endocarditis valvular aguda, y en 2 valvulitis sifilítica de la aorta. Hubo 3 casos cada uno de pericarditis tuberculosa adhesiva crónica, y de pericarditis aguda no tuberculosa. Las infecciones pulmonares no tuberculosas parecen constituir un factor de importancia en la etiología de la miocarditis intersticial. Los infartos miliares predominaron en los corazones hipertrofiados, en los corazones con arterioesclerosis coronaria grave, y en las últimas décadas de la vida. El estudio no apoyó la teoría de un corazón pequeño en la tuberculosis. La hipertrofia ventricular derecha fué muy rara. La medición de la pared ventricular pareció constituir una pauta poca fidedigna para la hipertrofia; el aspecto microscópico de las fibras miocardíacas pareció ser más exacto. La desproporción moderada o intensa entre el pulso y la temperatura indica afección miocardíaca. Observáronse con bastante frecuencia soplos debidos a lesiones valvulares orgánicas. Los soplos funcionales fueron raros. El estudio no apoya la hipótesis de que la hipertensión y la tuberculosis activa son incompatibles. Los trazados electrocardiográficos rinden con frecuencia hallazgos significativos. Aunque la serie actual es demasiado pequeña para permitir sacar conclusiones bien definidas sobre muchos puntos que se prestan a controversia, los autores opinan que la mayor atención prestada al sistema cardiovascular del tuberculoso, culminará en un cálculo más exacto de la lesión cardíaca existente.

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AIR EMBOLISM[1]

An Alternate Concept of Its Origin in Pneumothorax. Its Prevention and Treatment

J. G. BOHORFOUSH[2]

Air embolism following pneumothorax has been attributed to air entering the pulmonary vein and passing through the heart into the arterial system. This concept is not substantiated by the manifestations of this syndrome in all cases. On the whole, this explanation has been only partially satisfactory. Air is not found constantly in the heart or carotid arteries at autopsy, nor has the method by which air enters the pulmonary vein been adequately clarified. The following cases constitute our experience with this accident in over 10,000 inductions.

CASE REPORTS

Case 1: A Negro, thirty-three years of age, with bilateral moderately advanced pulmonary tuberculosis, was reaching the arrested stage after six months of left pneumothorax. On a routine refill, with adequate novocaine anaesthesia, he was punctured twice, the first time with a 16 gauge needle. Because of pain this was removed without the introduction of any air. The usual 19 gauge needle was then introduced into the pleural cavity. Corrected pressure readings were −4 −10. After 200 cc. of air had been introduced, he began to complain of pain in the chest wall. The pressures at this time were −3 −6. Another 100 cc. of air was introduced, the pressures rose to −2 −5 and the pain became severe. The refill was then discontinued. He immediately sat up for a few seconds and then proceeded to get into a wheel chair. He suddenly grasped his chest, cried out and fell in a tonic convulsion. He was placed in the Trendelenburg position and oxygen was administered. Coramine was given intramuscularly twice. The convulsions soon became clonic in character. He developed Cheyene-Stokes respiration with deep cyanosis during the periods of apnoea. The heart was tumultuous, but no evidence of intracardial air was obtained. Frothy, blood-tinged sputum appeared at the lips. Thirty minutes after onset, he died. Autopsy failed to reveal any evidence of injury or puncture of the lung. No air was found in the heart. Only a few uninjured adhesions at the apex were noted. There were none at the site of either puncture. A larger than usual number of bubbles was noted in the veins on the surface of the brain. A small subparietal pleural haemorrhage was noted at the site of the first puncture. No evident method for passage of air by way of the pulmonary vein was found. Yet, this patient was dead from air embolism following pneumothorax.

Case 2: A white female, thirty-five years of age, with moderately advanced tuberculosis, was receiving bilateral pneumothorax. The right lung was expanding involuntarily and, on a routine refill of this side, trouble was encountered. The manometric readings were unsatisfactory. After 20 cc. of air had been given, she began to complain of pain and the refill was discontinued. She rose immediately, put on her dressing gown and walked about fifteen feet before she grasped her right side and fell in a tonic convulsion. Her head and trunk were placed at an angle of 70 to 80 degrees below the horizontal and

[1] Published with the permission of the War Department and the Surgeon General's Office.

[2] Major, Medical Corps, Station Hospital, Goodfellow Field, San Angelo, Texas.

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Air embolism following pneumothorax has been attributed to air entering the pulmonary vein and passing through the heart into the arterial system. This concept is not substantiated by the manifestations of this syndrome in all cases. On the whole, this explanation has been only partially satisfactory. Air is not found constantly in the heart or carotid arteries at autopsy, nor has the method by which air enters the pulmonary vein been adequately clarified. The following cases constitute our experience with this accident in over 10,000 inductions.

CASE REPORTS

Case 1: A Negro, thirty-three years of age, with bilateral moderately advanced pulmonary tuberculosis, was reaching the arrested stage after six months of left pneumothorax. On a routine refill, with adequate novocaine anaesthesia, he was punctured twice, the first time with a 16 gauge needle. Because of pain this was removed without the introduction of any air. The usual 19 gauge needle was then introduced into the pleural cavity. Corrected pressure readings were −4 −10. After 200 cc. of air had been introduced, he began to complain of pain in the chest wall. The pressures at this time were −3 −6. Another 100 cc. of air was introduced, the pressures rose to −2 −5 and the pain became severe. The refill was then discontinued. He immediately sat up for a few seconds and then proceeded to get into a wheel chair. He suddenly grasped his chest, cried out and fell in a tonic convulsion. He was placed in the Trendelenburg position and oxygen was administered. Coramine was given intramuscularly twice. The convulsions soon became clonic in character. He developed Cheyene-Stokes respiration with deep cyanosis during the periods of apnoea. The heart was tumultuous, but no evidence of intracardial air was obtained. Frothy, blood-tinged sputum appeared at the lips. Thirty minutes after onset, he died. Autopsy failed to reveal any evidence of injury or puncture of the lung. No air was found in the heart. Only a few uninjured adhesions at the apex were noted. There were none at the site of either puncture. A larger than usual number of bubbles was noted in the veins on the surface of the brain. A small subparietal pleural haemorrhage was noted at the site of the first puncture. No evident method for passage of air by way of the pulmonary vein was found. Yet, this patient was dead from air embolism following pneumothorax.

Case 2: A white female, thirty-five years of age, with moderately advanced tuberculosis, was receiving bilateral pneumothorax. The right lung was expanding involuntarily and, on a routine refill of this side, trouble was encountered. The manometric readings were unsatisfactory. After 20 cc. of air had been given, she began to complain of pain and the refill was discontinued. She rose immediately, put on her dressing gown and walked about fifteen feet before she grasped her right side and fell in a tonic convulsion. Her head and trunk were placed at an angle of 70 to 80 degrees below the horizontal and

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[1] Published with the permission of the War Department and the Surgeon General's Office.

[2] Major, Medical Corps, Station Hospital, Goodfellow Field, San Angelo, Texas.

oxygen and stimulants were administered. The convulsions soon became clonic in character. She developed Cheyne-Stokes respiration, with deep cyanosis during the periods of apnoea. Blood-streaked, frothy sputum appeared at the lips. The heart was tumultuous, but no evidence of intracardial air was obtained. She recovered in fifteen minutes.

In addition to the above cases, we have had the opportunity to observe 6 others. All except one exhibited essentially the same phenomena, and they may be summarized as follows:

1: There is usually pain in the chest during the induction of air.
2: The onset is after the patient assumes the vertical position.
3: There is a latent period of a few seconds before the onset of cerebral symptoms.
4: There is usually a cry, followed by unconsciousness and convulsions, remarkably resembling epilepsy. This undoubtedly is a central nervous system manifestation. The blood in the sputum is probably due to injury of the mouth following the powerful masticating movements.
5: The only effective method of treatment is the lowering of the head and trunk.

In our experience, we have never seen emboli that could be interpreted as other than cerebral. Other observers have reported emboli to other parts of the body, notably Durant's case of air embolism (cited by Barnwell) revealing electrocardiographic changes three hours after the accident. We do not doubt that in the cases in which air enters the pulmonary circulation emboli occur in many portions of the body. However, we do not feel that this is a very frequent occurrence. Pain has been observed in 7 of the 8 cases seen by us but is not mentioned as a frequent event by others.

DISCUSSION

In cases similar to those reported above, it seemed unlikely that the air was arterial borne. The force of a bubble of air is probably of little or no moment in the powerful arterial stream, and embolism should occur not only in the vertical but in any position. If the air arriving at the carotid artery awaited the force of gravity to rise to the brain, we should have in this condition a comparatively large incidence of coronary occlusion. However, the symptoms suggest brain embolism.

In the swift moving arterial stream there would be no need for a latent period of a few seconds before onset of symptoms. Less than a second would be required to carry the blood to the brain. These facts indicate that the air enters a low tension system where the force of gravity is comparatively great, and in which the air would not be thrown into the brain, but float upward when the patient assumes the vertical position.

In spontaneous pneumothorax, were there is direct communication between the lung and the air in the pleural cavity, air embolism does not ensue. The injured lung and the high intrapleural pressure are the ideal conditions postulated for this accident. While this observation is not conclusive, it points toward some other mechanism as the predominant cause of this condition.

Air embolism from a needle entering or tearing an adhesion has been described. Maendl (quoted by Barnwell) records a case of intermittent embolism due to an open vessel in an adhesion. It is difficult for us to see how air enters the pulmonary circulation from an adhesion when the pleura is drained by vessels emptying into the superior vena cava.

The venous system of the brain in a considerable portion drains upward into the longitudinal sinus. Lowering the head after the occurrence of air embolism would empty this sinus of air, but certainly not its tributary veins, which are not draining downward. With the increase in venous pressure in this position, it would be more difficult to empty the capillaries and veins of the incoming air from the arterial side. If the classical theory is correct, either this must happen, or the air rises against the arterial stream and returns to the aortic valve. The potentialities for coronary occlusion again become evident.

Inasmuch as the clinical picture of air embolism following pneumothorax is not that of shock and is one of central nervous system aberration, we can safely assume that air reaches the brain tissues. As the arterial transmission of air fails to clarify the phenomena in all cases, an alternate route was postulated. In these cases, the course of the air must be through a low tension system affected by gravity, in which the air would rise when the patient assumes the vertical position. The venous system meets these specifications *in toto*. In this system, without peregrination through the heart and arteries, are two routes to the cranial cavity. First, by the system of veins draining into the superior vena cava and, second, by way of the vertebral system of veins described by Batson. Reference to any standard textbook of anatomy reveals that the entire thoracic wall and pleura is emptied of blood by way of the internal mammary, highest intercostal, the azygos, hemiazygos and the accessory hemiazygos veins into the superior vena cava. For a description of the magnitude and importance of the vertebral system of veins, reference should be made to the original work of Batson. Neither the valveless vertebral system of veins nor the caval system of veins offers any resistance to the flow of air under low tension. The flow of air in the caval system is in the direction of the flow of blood. Upon assuming the vertical position, the air, having reached either the superior vena cava or the vertebral veins, rises to the sinuses of the cranial cavity. It takes less imagination to visualize, in the rigid, valveless cranial system, this air becoming compressed to a pressure over that of the capillaries than to postulate a bubble of air remaining in the aorta until the patient assumes the vertical position. This concept more easily explains the latent period between the rising of the patient and the onset of symptoms.

CONCLUSION

Air embolism is one of the most terrifying and potentially dangerous accidents that attends puncture of the chest wall. Some measures adopted by us to lessen its occurrence and mortality had to be reviewed in the light of venous transmission of the embolus, before a rational reason for them could be found in some cases. We had learned from bitter experience that any unusual or severe pain

in the chest wall during pneumothorax was often a premonitory sign of air embolism. If the arterial transmission of air occurred, there was little that could be done. We found, however, that if we lowered the patient's head and trunk we never encountered air embolism. We have felt that we have avoided air embolism on several occasions by this simple procedure. In the 2 cases reported above, this sign went unheeded.

In the treatment of this condition, we found the usual Trendelenburg position insufficient; the patient must practically be stood on his head. The whole of the superior vena cava must be brought below the level of the heart in order to completely empty it of air. In 8 consecutive cases treated by this procedure all recovered.

The hazard of air embolism is considered to be greater in the aspiration of fluid than in the induction of air. The onset of symptoms is usually rapid in these cases, and occurs while the procedure is being carried out on the sitting patient. The author has had no personal experience with this mishap. Relying on the description of others of this phenomenon, it is found that one of two things has occurred previous to the onset of symptoms. Either a large amount of fluid has been withdrawn, without the replacement of air, or no fluid has been withdrawn. In the first condition, it must be demonstrated that a shift in the mediastinum has not occurred, before a diagnosis of air embolism can be made. In the case where no fluid has been withdrawn, it seems more plausible to assume that air entered through a vein in the chest wall, the needle not entering the pleural cavity. In trying to ascertain the cause of air embolism in these cases, it is usually found that the syringe had been removed from the needle to "remove a plug," or worse and more frequent, a small amount of air had been introduced into the needle "to open it." It is almost inconceivable that a chest full of fluid could be passed through, the lung pierced or injured and the fluid never found. If such an occurrence did happen, with the low tension in the alveolus, and the high pressure of the fluid in the pleural cavity, fluid rather than air would enter both the alveolus and the pulmonary vein. However, the dilated veins of the inflamed pleura can easily be a mode of transmission of air.

The almost inevitable conclusion to be drawn from the above course of events is that in these cases the air enters the venous system in the thoracic wall (the possibility of the bronchial vein seems remote) and passes to the superior vena cava or the vertebral veins and, thence, to the cranial cavity. This hypothesis clarifies symptoms seen in many cases and unexplained by the older theory.

From this conclusion, procedures in treatment and prevention of air embolism became clarified. Those enumerated below have in the most part been described in previous works, some of them are postulated on the venous hypothesis of air transmission. We have found that they are all useful.

(*1*) Never give any amount of air unless proper readings are obtained. The reasoning that one is in a small pocket, and therefore the pressures are neutral, is fallacious. In a small pocket the pressures are usually highly negative with wide oscillations. If it is felt that the needle is in the pleural cavity and that readings are not being obtained because of technical difficulties, the needle

should be removed and then the proper remedies applied. Within the chest wall is no place to overcome mechanical difficulties. Small oscillations of the manometer are not only not satisfactory readings, but are an absolute contra-indication to the administering of air or any other procedure except the removal of the needle; the needle is more likely in a vein or an alveolus.

(*2*) At the first indication of unexplained or unusual pain the needle should be removed and the head and trunk lowered. Any other procedure is courting the danger of an air embolism. A pneumothorax can always be attempted later.

(*3*) In the aspiration of fluid, first locate the fluid with a small syringe (2 cc.) and as small a gauged needle as is compatible with the viscosity of the fluid. Never inject air or remove the syringe from the needle until fluid has been aspirated. If it is felt that the needle is occluded, remove the needle and syringe together. Overcome technical difficulties outside the chest wall. If blood is aspirated, do not assume the needle is in the pleural cavity, the probabilities are that it is in a vein of the hyperaemic pleura. The author has aspirated blood thinking that he had encountered a haemothorax, only a second later to insert the needle a centimeter further and find the fluid clear.

(*4*) In air embolism the head and trunk should be lowered to a steep angle below the horizontal; the entire superior vena cava should be below the heart, and oxygen, which sould be immediately available, should be administered continuously. Other supportive measures are applied as necessary.

SUMMARY

1. Two cases of air embolism following pneumothorax have been described. Autopsy of the fatal case failed to reveal any injury to the lung.

2. Air embolism was, in these cases, characterized by pain in the chest during the induction of air, onset of symptoms after the vertical position has been assumed and a latent period of a few seconds between the time of rising and the onset of symptoms. The clinical manifestations are similar to an attack of epilepsy, characterized by convulsions, Cheyne-Stokes respiration and tumultuous heart action. Treatment should consist of lowering the head and trunk until the entire superior vena cava is below the heart level.

3. In view of the above findings, the transmission of air through the pulmonary veins in all cases is doubtful. An alternate route was then postulated. The air may enter the veins in the thoracic wall and, thence, reach the cranial cavity through the superior vena cava or the vertebral system of veins.

4. The following suggestions are made for the prevention and treatment of this condition. Never give air unless the manometric readings are satisfactory. Technical difficulties should be corrected after removing the needle from the thoracic wall. At the first indication of unexplained or unusual pain the needle should be removed and the head and trunk lowered. In aspirating fluid the syringe should not be removed from the needle, or air introduced until fluid has been aspirated. If air embolism occurs, it is necessary to lower the head and trunk until the superior vena cava is below the level of the heart.

SUMARIO

1. Descríbense dos casos de embolia aérea consecutiva al neumotórax. La autopsia del caso letal no reveló ninguna lesión pulmonar.

2. En estos casos la embolia aérea se caracterizó por dolor en el tórax durante la introducción del aire, iniciación de los síntomas después de tomarse la posición vertical, y un período latente de algunos segundos entre el momento de levantarse y la iniciación. Las manifestaciones clínicas son semejantes a un ataque de epilepsia, caracterizado por convulsiones, respiración de Cheyne-Stokes y tumultuosa acción cardíaca. El tratamiento debe consistir en inclinar la cabeza y cuerpo hasta que la cava superior quede debajo del nivel cardíaco.

3. En vista de los hallazgos anteriores, parece dudoso el paso del aire a través de las venas pulmonares en todos los casos, por lo cual se postuló una vía alternada: El aire puede penetrar en las venas de la pared torácica, y de allí llegar a la cavidad craneal a través de la cava superior o de las venas de la región vertebral.

4. Ofrécense las siguientes indicaciones para la prevención y tratamiento del estado: No se introduzca jamás aire a menos que sean satisfactorias las lecturas manométricas; corríjanse las dificultades técnicas después de extraer la aguja de la pared torácica; al primer signo de dolor inexplicado o inusitado extráigase la aguja e inclínense la cabeza y tronco; al aspirar líquido no se separe la jeringa de la aguja, ni se introduzca aire sino después de aspirarse el líquido; si se presenta embolia aérea es necesario inclinar la cabeza y tronco hasta que la cava superior quede debajo del nivel del corazón.

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DIAPHRAGMATIC PARALYSIS AND THE CLOSURE OF TUBERCULOUS CAVITIES[1]

RICHARD T. ELLISON AND C. ROBERT TITTLE

When section of the phrenic nerve for the purpose of artificially paralyzing the diaphragm was introduced by Stuertz (1), it was found that as a result of this procedure a partial collapse of the lung was frequently obtained amounting to from one-fourth to one-third its volume (2). For this reason it was hoped that induced diaphragmatic paralysis would be of great help in the management of tuberculosis in the lung lying above. Although it was anticipated that the effects of paralyzing the diaphragm would be most marked in the lower half of the chest, and therefore the procedure would be of greatest value in lower lobe lesions, these expectations were only in part borne out by subsequent experience. Nehil and Alexander (3) report 40 per cent closure of cavities in the upper third of the lungs in a series of cases subjected to phrenic nerve interruption, whereas only 29 per cent of cavities located in the lower third of the lungs were closed by the same procedure. These authors, among others, believe that, following induced hemidiaphragmatic paralysis, a tuberculous lesion may be favorably affected regardless of position. Somewhat better results were obtained by the addition of artificial pneumoperitoneum to the diaphragmatic paralysis (4), but a recent reveiw of the immediate and late results following phrenic nerve interruption in more than 100 cases (5) led to the conclusions that the value of this procedure in the collapse therapy program of pulmonary tuberculosis depends largely upon the proper selection of cases.

The purpose of this paper is to discuss the effect of a rise in the diaphragm on tuberculous cavities situated in various parts of the lung above, and to inquire into the factors that lead to the success or failure of the procedure as a means of closing them. Roentgenograms of selected cases will be used as a basis for the discussion.

Van Allen (6) has illustrated that when the diaphragm rises following paralysis, resulting in a reduction of the long diameter of the hemithorax, the loss of volume is not distributed uniformly throughout the lung. Rather, the slack is taken up mostly by the diseased area and a selective type of collapse results. The mechanism of selective collapse has been previously discussed by one of us (7). Although this explanation may be applied to infiltrative lesions in which there is a considerable amount of uninvolved pulmonary tissue still present, it seems inadequate to account for the closure of large cavities. Coryllos, in discussing the mechanics of tuberculous cavities (8), stressed the importance of collapse of the draining bronchus in cavity closure. Perhaps this factor is more important than selective collapse in explaining the success or failure of therapeutic measures, especially in those cases of round or oval cavities in which the intracavitary pressure is above atmospheric pressure. As was noted above, Nehil and Alexander

[1] From the Pulmonary Chest Clinic, Graduate Hospital, University of Pennsylvania, Graduate School of Medicine, Philadelphia.

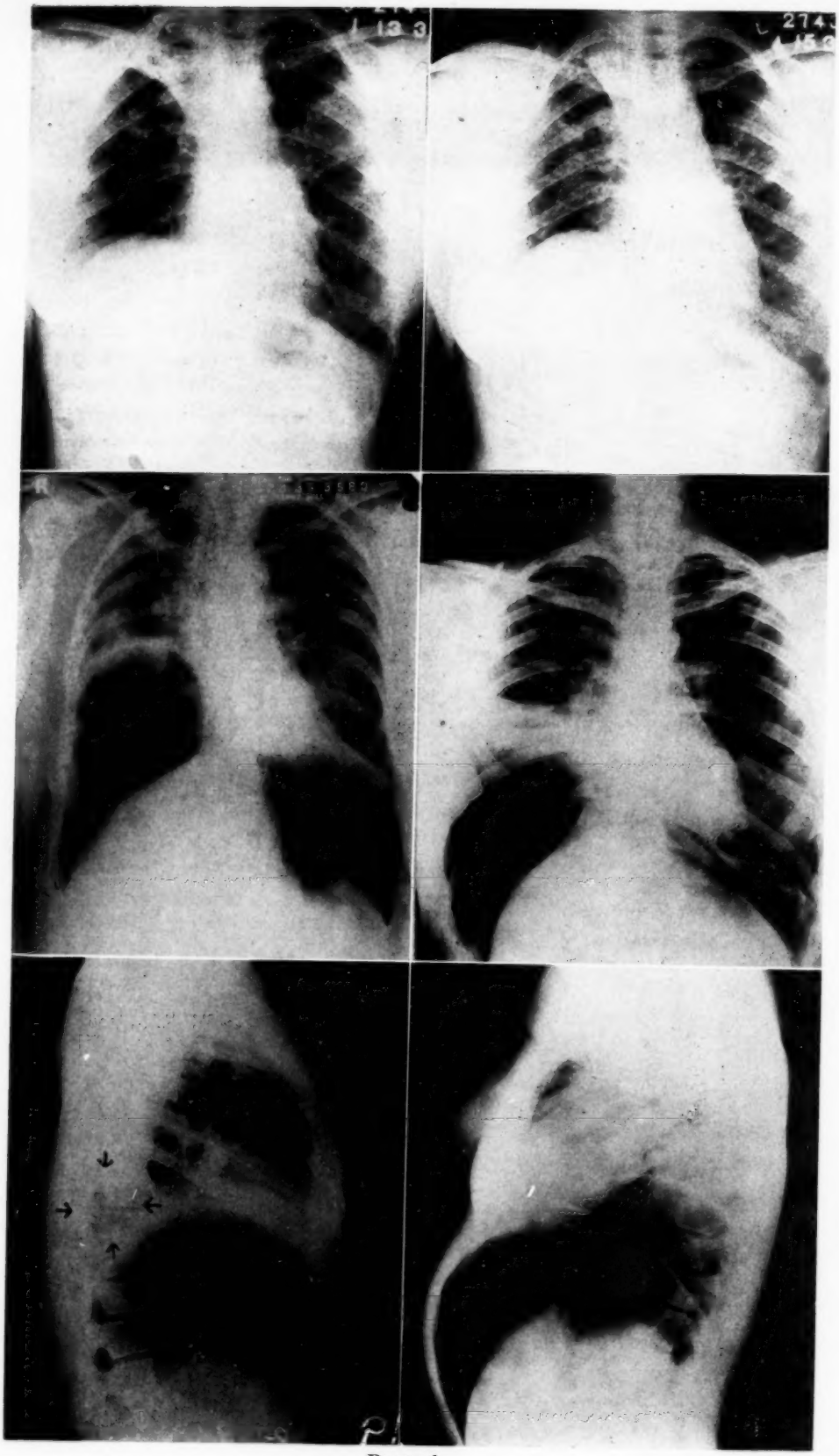

PLATE 1
FIGS. 1–6

found that cavities in the upper third of the lungs close more frequently following phrenic paralysis than cavities in the lower third. These authors however do not divide their figures in right- or left-side cavities. In speaking of the arrest of all types of lesions by phrenic paralysis, they found "virtually no difference between the results in the left-sided and right-sided cases." In a small series of cases under our own care, however, we noted that cavities in the upper part of the right lung closed more frequently than cavities in the upper part of the left lung following paralysis of the corresponding half of the diaphragm. Of 12 cases with right apical cavities, 6, or 50 per cent, closed following right diaphragmatic paralysis. Of 9 cases with left apical cavities, 3, or 33 per cent, closed following paralysis of the left half of the diaphgragm. More specifically it was noted that closure on the right was frequently the result of atelectasis of the whole upper lobe and a fanning up of the lobe against the upper mediastinum (figures 1 and 2). This particular type of cavity closure was never seen on the left side and may account for the better results on the right.

The situation in each hemithorax, from the point of view of the physics involved, is as follows: The musculature of the diaphragm is in a constant state of tension even when not actively contracting and this force opposes the elastic recoil of the lungs and keeps the pulmonary tissues continually on the stretch. The diaphragmic musculature also opposes the positive intraäbdominal pressure created by the contraction of the muscles of the abdominal wall and prevents the transmission of this pressure to the contents of the rigid thoracic cage. When one-half of the diaphragm is paralyzed it rises into the thorax because of the pull of elastic tissue from above and, especially with pneumoperitoneum, because of a positive push from below. The effect of this on cavities depends on their location. If the cavity is in the lower two-thirds of the lung there is usually a considerable amount of resilient lung substance on all sides of it and closure is

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FIGS. 1 & 2 (first row). Case 1. A. N. Phrenic exairesis performed January 10, 1931, in an attempt to collapse a cavitary lesion of the right upper lobe. Figure 1 shows a satisfactory immediate rise in the diaphragm with the cavity still open. X-ray film on April 15, 1931 (figure 2) shows cavity closed and upper lobe compressed fan-like against the mediastinum due to atelectasis and/or fibrosis.

FIG. 3 (middle left). Case 2. M. L. Cavity in the right lower lobe which has "ridden up" on a paralyzed diaphragm, failing to collapse even after the addition of pneumoperitoneum.

FIGS. 4 (middle right) & 5 (bottom left). Case 3. E. L. Phrenic crush on right side in July, 1939, for tuberculous cavity in right lower lobe, followed by pneumoperitoneum three months later. X-ray film taken September 30, 1939 (figure 4) shows cavity not influenced by a satisfactory rise of the diaphragm. In a lateral view (figure 5) the cavity is seen to be located in the triangular space behind the dome of the diaphragm, and the apex of the dome of the paralyzed right diaphragm is anterior to the vertical plane through the hilum.

FIG. 6 (bottom right). Case 4. M. M. Left phrenic crush done January 4, 1939, followed by induction of pneumoperitoneum for tuberculous infiltration in left upper lobe. The postero-anterior view shows satisfactory rise in the left diaphragm. The lateral view (figure 6) shows how the heart lies in front of the dome of the left diaphragm, the apex of the dome lying behind the midline, and that the posterior triangular area is obliterated.

chiefly the result of relief of outward pull of elastic tension on its walls. If the cavity is in the apex, however, there is less resilient lung above it and the loss of tone of the diaphragmatic muscle allows the positive intraäbdominal pressure to neutralize the entire elastic recoil of the lung on that side. There is then a positive pressure in that half of the thoracic cage and the cavity is forced against the rigid walls of the cupola of the thorax.

This concept offers an explanation of the successful closure of apical cavities following a diaphragmatic rise, but it does not help to explain why the results are more satisfactory in the right apex. The answer to this problem might be found in a consideration of the anatomical differences of the two sides. The anatomy of the right hilar region differs from that of the left in at least three respects. First, the angle that the right main stem bronchus makes with the line of the trachea is much greater than the angle formed by the left main stem bronchus. Second, the relation of the bronchi to the pulmonary blood vessels differs on the two sides. The bronchus to the right upper lobe rises above the point where the pulmonary artery crosses the main stem bronchus, being termed the eparterial bronchus. On the left the main stem bronchus does not divide until beyond the point of crossing of the artery. Third, there are more lymphatic nodes about the right hilum, and especially the upper lobe bronchus, than there are on the left side. As a result of these anatomical peculiarities, it is our belief that a marked rise in the diaphragm on the right side frequently leads to a kinking or pinching off of the eparterial bronchus, resulting in atelectasis of the right upper lobe and in this way closure of the cavity. Thus, the mechanism of direct pressure and the closure of the eparterial bronchus help to explain the successful effect of diaphragmatic rise on lesions in the upper right lung.

It has also been observed clinically that cavities in the lower lobes frequently are uninfluenced even by a satisfactory elevation of the diaphragm and that this is especially true in the right lower lobe. Factors which we believe contribute to these unfavorable results in the lower lobe will now be discussed.

First is the fact that without counterpressure a cavity in either lower lobe may ride up on the elevated diaphragm, like a bubble on a wave, without any reduction in size (figure 3). Second, when the diaphragm rises following paralysis, it is only a further stretching upward of the dome above its attachments, these attachments remaining immobile. This results in exaggeration of the normal triangular space lying behind the dome of the diaphragm. If the lung is adherent to the sides of the costophrenic sulcus it cannot escape from this triangular space as it normally does during expiration, and little or no effect is noted on cavities lying in this portion of the lower lobe (figures 4 and 5). There is one other factor that makes the right lower lobe the most unfavorable site of all. When viewed in a true lateral projection, it is evident that the apex of the dome of the diaphragm on the right side is anterior to a vertical plane through the hilum (figure 5). On the left side, however, the heart lies in the anterior half of the chest and the diaphragm has to pass under it before it can begin any appreciable rise. This pushes the apex of the dome behind the midline, thereby reducing the size of the triangular space behind the left diaphragm (figure 6).

SUMMARY

1. An attempt has been made to explain the success or failure of diaphragmatic paralysis in the closure of tuberculous cavities with special emphasis on the location of the cavity.

2. Contrary to expectations, upper lobe cavities often are more favorably influenced by rise of the diaphragm than are similar lesions in the lower lobes and this is especially true of cavities in the right upper lobe. Factors accounting for these results are discussed.

3. Finally, an attempt has been made to explain why lower lobe cavitary lesions, especially those in the right lower lobe, frequently fail to respond to a satisfactory elevation of the diaphragm.

SUMARIO

1. Tratáse de explicar el éxito o fracaso de la parálisis diafragmática en el cierre de las cavernas tuberculosas, recalcando en particular la localización de la caverna.

2. En contraposición a lo esperado, la elevación del diafragma afecta a menudo más favorablemente las cavernas del lóbulo superior derecho que lesiones semejantes de los lóbulos inferiores, rezando esto en particular con las cavernas del lóbulo superior derecho. Discuténse los factores que explican estos resultados.

3. Tratáse por fin de explicar por qué las lesiones cavitarias del lóbulo inferior, en particular las del lóbulo inferior derecho, con frecuencia no responden a la elevación satisfactoria del diafragma.

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VITAMIN NUTRITION IN TUBERCULOSIS[1,2,3]

HORACE R. GETZ AND THEODORE A. KOERNER

Vitamin nutrition is only a part of the problem in nutrition presented in tuberculosis patients. Recent work suggests that it is a major problem, however, because vitamin deficiencies in tuberculous persons are frequent and often profound (1, 2, 3). The lack of practical clinical laboratory tests for some of the vitamins has limited our knowledge about them, but we have such tests for both vitamin A and ascorbic acid. The tests have been applied to both tuberculous and nontuberculous subjects, providing a basis for comparison. The exact significance of the various blood levels of these vitamins is not known, but it is evident that tuberculous patients have lower blood levels of both vitamins than nontuberculous subjects, and patients with advanced tuberculosis often have profound deficiencies.

This is disturbing because the sanatorium diet is usually planned to be adequate and malnutrition is thought to be a problem only in cases of gastrointestinal disease. The nutritional status of a patient can no longer be judged by weight and appearance, for nutrition tests reveal vitamin deficiencies in overweight as well as underweight patients. It is true, however, that an underweight person is more apt to have a dietary deficiency.

The first workers to find vitamin A deficiency in tuberculous patients used the biophotometer, as there was no practical blood test at that time (4, 5). Our first efforts with this instrument revealed that 53 per cent of the tuberculous subjects were deficient in vitamin A, as contrasted with 6 to 11 per cent in nontuberculous control groups. Later, 20 of the same sanatorium patients were tested for vitamin A in the plasma. On the basis of our present evaluation of the blood levels of vitamin A, 13 of the 20 had normal blood levels and 4 were deficient. Many of the observed levels were just above our designated minimal normal level; if a higher standard (as that of Wagner (6)) is used, only 3 of the 20 had normal plasma levels.

The subjects in the present report were patients attending, for the first time, the chest clinic of the Henry Phipps Institute. More than twice as many Negroes as white people were tested. Persons of Italian descent comprised the largest nationality group among the white patients. About half of the Negroes and a third of the white persons were dependent on public assistance for their living. Two hundred sixty-five subjects were used for this study; all came from the same economically underprivileged areas of Philadelphia, except 27 staff members who were used as control subjects.

The methods employed for testing were the same as those described in a previous publication and the figures given include those previously published (2).

[1] Presented before the Medical Section at the 38th annual meeting of the National Tuberculosis Association, Philadelphia, May 8, 1942.

[2] From the Henry Phipps Institute, University of Pennsylvania, Philadelphia.

[3] Aided by a grant from the John and Mary R. Markle Foundation.

The Evelyn photoelectric colorimeter was used for the measurement of the Carr-Price reaction of vitamin A, and the plasma filtrate reduction of 2,6 dichlorophenolindophenol to determine ascorbic acid. The results of the vitamin A tests are recorded in International Units per 100 cc. of plasma and the ascorbic acid as mg. per 100 cc. of plasma.

RESULTS OF TESTS FOR VITAMIN A

To interpret the results of the vitamin A tests, an evaluation standard is needed. To meet this need we have attempted to set up a minimal normal plasma level of vitamin A and also to set a level below which observed plasma levels would indicate pathological deficiency. This leaves an intermediate or borderline group in which observations on the plasma level are at present difficult to interpret because of insufficient knowledge. Table 1 gives the ranges of the three plasma levels and also adjusts for the sex difference described by Kimble (7) and by Scalongne (8). This interpretation of the plasma levels is largely empiric at present, but new data are being accumulated which may eliminate the borderline group.

TABLE 1

SEX	PLASMA LEVELS OF VITAMIN A IN INTERNATIONAL UNITS PER 100 CC.		
	Normal	Borderline	Pathologically deficient
Male	110 and above	85–110	Below 85
Female	95 and above	75–95	Below 75

In figure 1 the observed plasma level of vitamin A is plotted against age for each subject group tested. In table 2 the percentages of each subject group in the various plasma levels are given. The poor showing of the "just-diagnosed" tuberculous cases is shown in table 3 in relation to the extent of the tuberculous involvement.

In table 4 the nontuberculous patient group has been broken up into its components and the percentage of each of these groups in the various plasma levels is given. The staff members, who have been added in table 4 to serve as better nourished nontuberculous controls, do show higher percentages in the normal plasma level than the nontuberculous patients; no staff member was pathologically deficient. In figure 3 the observations on the same nontuberculous patients are plotted to show more clearly race and sex differences. The distribution of the observations below the minimal normal plasma level has been tested statistically and reveals that the race and sex differences are significant. The median for the males is at 103 I.U., 96 I.U. for the females, 110 I.U. for the white subjects and 94 I.U. for the Negroes.

The patients in the nontuberculous group are the same in every other respect as the tuberculous group. They are friends, relatives and neighbors of the tuberculous patients and constitute the reservoir in which tuberculosis develops. About 50 per cent of this group came into the clinic because of upper respiratory

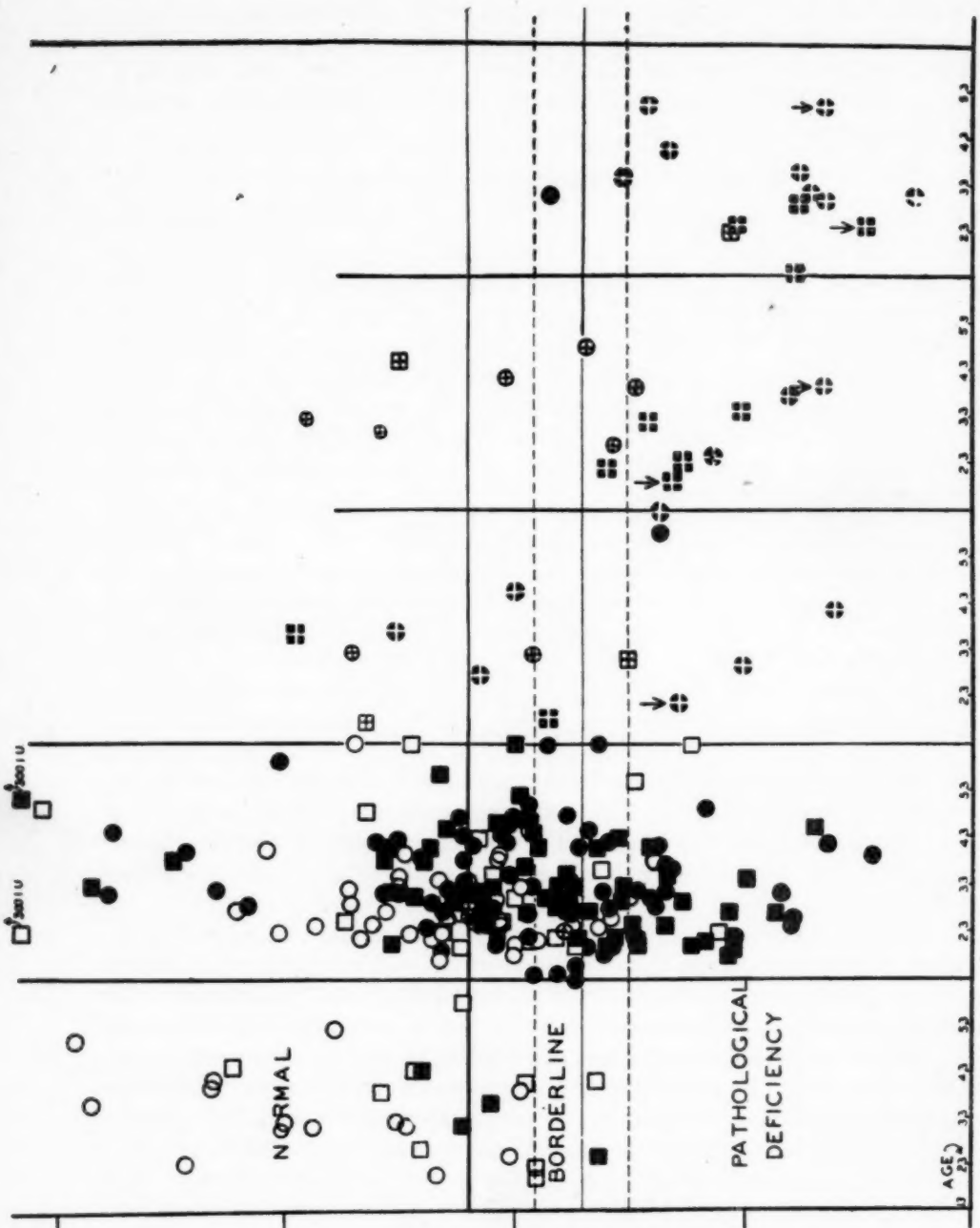

FIG. 1. Plasma vitamin A observations. Recently diagnosed pulmonary tuberculosis. Circles represent males; squares—females; solid symbols—Negroes. Tuberculous patients are plotted with crosses on the symbols. Arrows indicate persons dead of tuberculosis in five months.

symptoms. About 27 per cent had no symptoms, but came in for examination because of contact with a tuberculous person.

TABLE 2

Distribution of white and Negro patients on the basis of blood levels of vitamin A

PATIENT GROUP	NUMBER OF PATIENTS	NORMAL	BORDERLINE	PATHOLOGICALLY DEFICIENT
		per cent	*per cent*	*per cent*
White:				
Nontuberculous	64	59.3	28.1	12.5
Tuberculous just diagnosed	13	38.4	30.7	30.7
Negro:				
Nontuberculous	125	33.6	37.6	28.8
Tuberculous just diagnosed	30	6.6	13.3	80.0

TABLE 3

Distribution of tuberculous patients on the basis of blood levels of vitamin A and stage of tuberculosis

TUBERCULOUS PATIENT GROUP	NUMBER OF PATIENTS	NORMAL	BORDERLINE	PATHOLOGICALLY DEFICIENT
		per cent	*per cent*	*per cent*
Just diagnosed:				
Minimal	14	28.6	35.7	35.7
Moderately advanced	15	20.0	20.0	60.0
Far advanced	14	0.0	0.0	100.0

TABLE 4

Distribution of nontuberculous patients on the basis of blood levels of vitamin A and race and sex

NONTUBERCULOUS PATIENT GROUPS	NUMBER OF PATIENTS	NORMAL	BORDERLINE	PATHOLOGICALLY DEFICIENT
		per cent	*per cent*	*per cent*
White male	43	55.8	32.5	11.6
White female	21	66.7	19.0	14.3
Negro male	73	27.4	43.8	28.4
Negro female	52	42.3	28.9	28.9
Staff members (both races and sexes)	27	84.0	16.0	0.0

FIG. 1. Plasma vitamin A observations. Recently diagnosed pulmonary tuberculosis. Circles represent males; squares—females; solid symbols—Negroes. Tuberculous patients are plotted with crosses on the symbols. Arrows indicate persons dead of tuberculosis in five months.

RESULTS OF ASCORBIC ACID TESTS

In figure 2 the observed plasma level of ascorbic acid is plotted against age for each subject group. The distribution of observations is much different from that for vitamin A, as there are a number of cases in which no demonstrable ascorbic acid could be found. We have used 1 mg. per cent as the lowest minimal normal plasma level and all patients with plasma levels below 0.5 mg. per cent

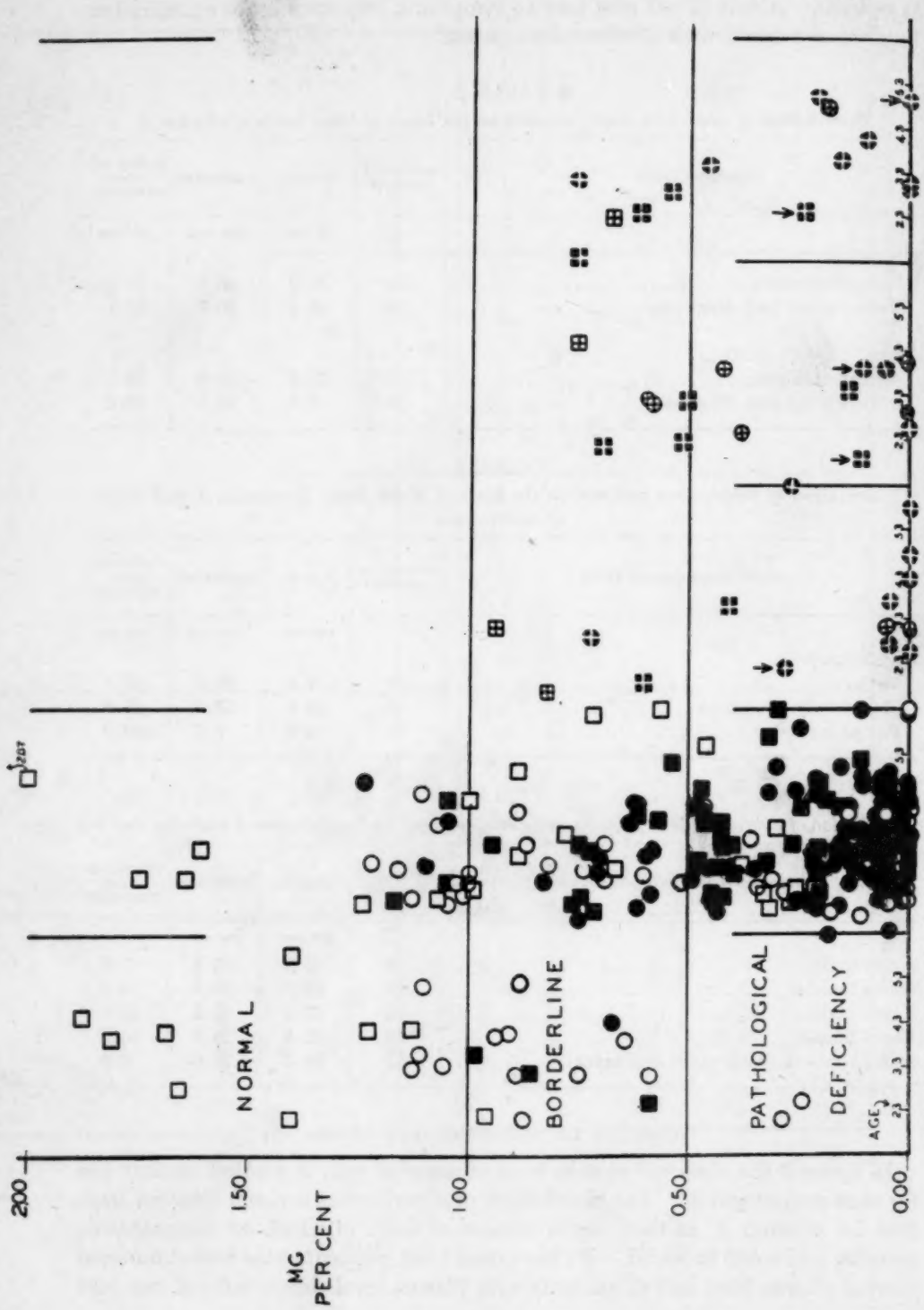

FIG. 2. Plasma vitamin C observations plotted with same symbols as in figure 1

are said to be pathologically deficient in ascorbic acid. Using this evaluation, the percentage of patients in each of the plasma levels is given in table 5.

The figures for the males and females in each group are presented separately because of the sex difference. In table 6 the observations on the "just-diag-

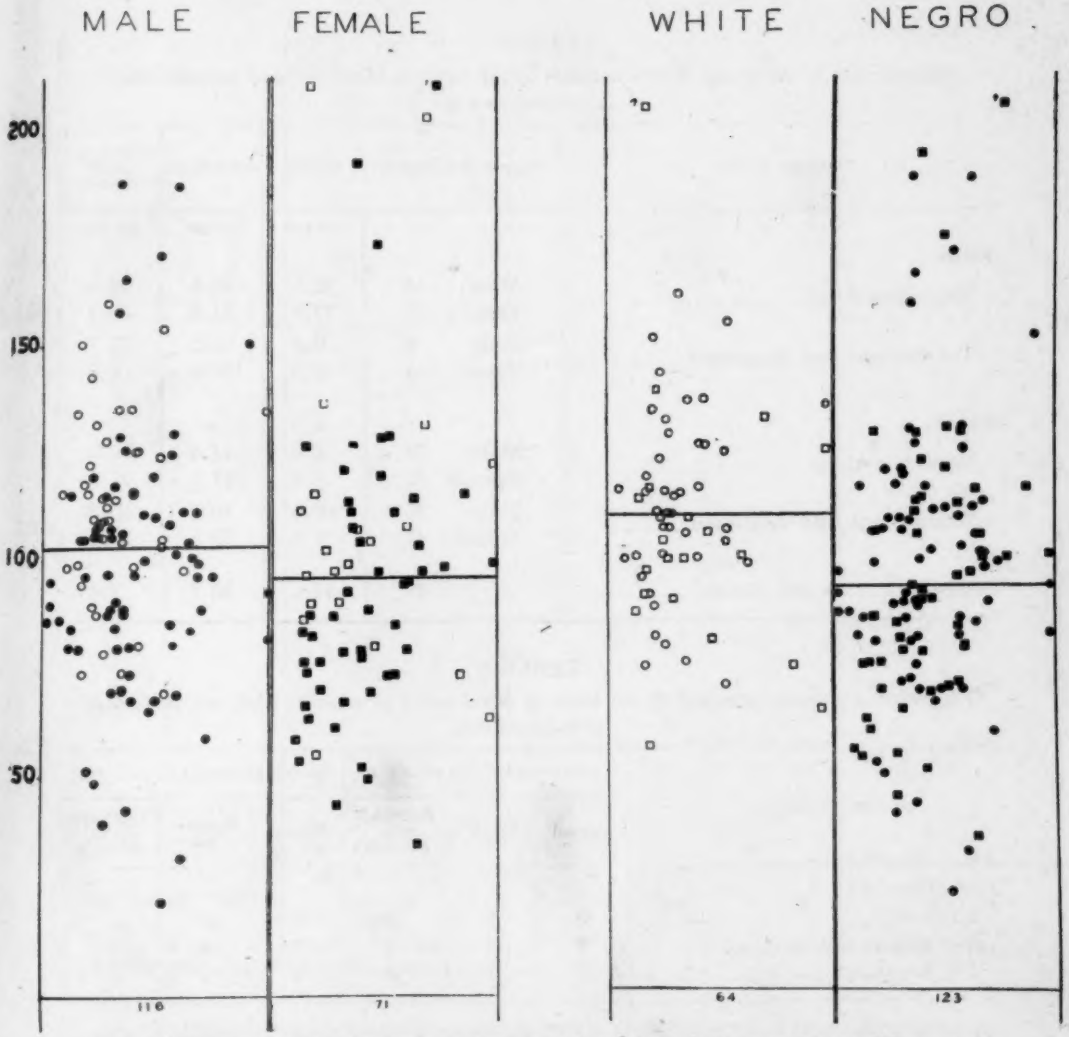

FIG. 3. Plasma vitamin A observations plotted to show the sex and race differences in the nontuberculous patients. The dividing line is the median line dividing the observations into halves. This mathematical expression of the average of the observed levels shows the differences in the patient groups.

nosed" tuberculous cases are given according to the stage of the tuberculous involvement. It is impossible to detect any relationship between the extent of the tuberculosis and the plasma level of ascorbic acid, as the values are so low and the number of patients too small.

In figure 4 the observations on the nontuberculous patients are plotted to show the sex and race differences more clearly. It is peculiar that the females should have the higher plasma levels of ascorbic acid, as shown by the median line. The median is at 0.17 mg. per cent for the males, 0.42 mg. per cent for the females, 0.47 mg. per cent for the whites and 0.21 mg. per cent for the Negroes.

TABLE 5

Distribution of white and Negro patients on the basis of blood levels of ascorbic acid, according to sex

PATIENT GROUP		NUMBER OF PATIENTS	NORMAL	BORDERLINE	PATHOLOGICALLY DEFICIENT
			per cent	*per cent*	*per cent*
White:					
Nontuberculous	Male	44	22.7	18.2	59.0
	Female	22	31.8	31.8	36.4
Tuberculous just diagnosed	Male	9	0.0	22.2	77.7
	Female	4	0.0	100.0	0.0
Negro:					
Nontuberculous	Male	76	3.9	14.4	81.5
	Female	52	5.8	17.3	77.0
Tuberculous just diagnosed	Male	20	0.0	10.0	90.0
	Female	11	0.0	63.6	36.4
Staff (both sexes and races)		27	44.4	48.1	7.4

TABLE 6

Tuberculous patients grouped on the basis of blood levels of ascorbic acid, sex and stage of tuberculosis

PATIENT GROUPS	MALES—NUMBER OF PATIENTS			FEMALES—NUMBER OF PATIENTS		
	Normal	Borderline	Pathologically deficient	Normal	Borderline	Pathologically deficient
Just diagnosed:						
Minimal	0	1	10	0	3	1
Moderately advanced	0	2	7	0	4	2
Far advanced	0	1	8	0	4	1

Statistical analysis of the distribution of observations below 0.5 mg. per cent reveals the race and sex differences to be highly significant.

COMMENT

The vitamin A level in the blood stream is fairly stable and is not affected by meals with the usual amounts of vitamin A present. If the peaks of fat absorption are avoided (three to six hours after eating) there is still less chance for error. This means that blood samples may be taken at any time without any

great error in the evaluation of nutritional status of vitamin A. The blood stream level of ascorbic acid rises much more quickly following a meal, the peak being between one and a half to three hours after eating. About a third of the

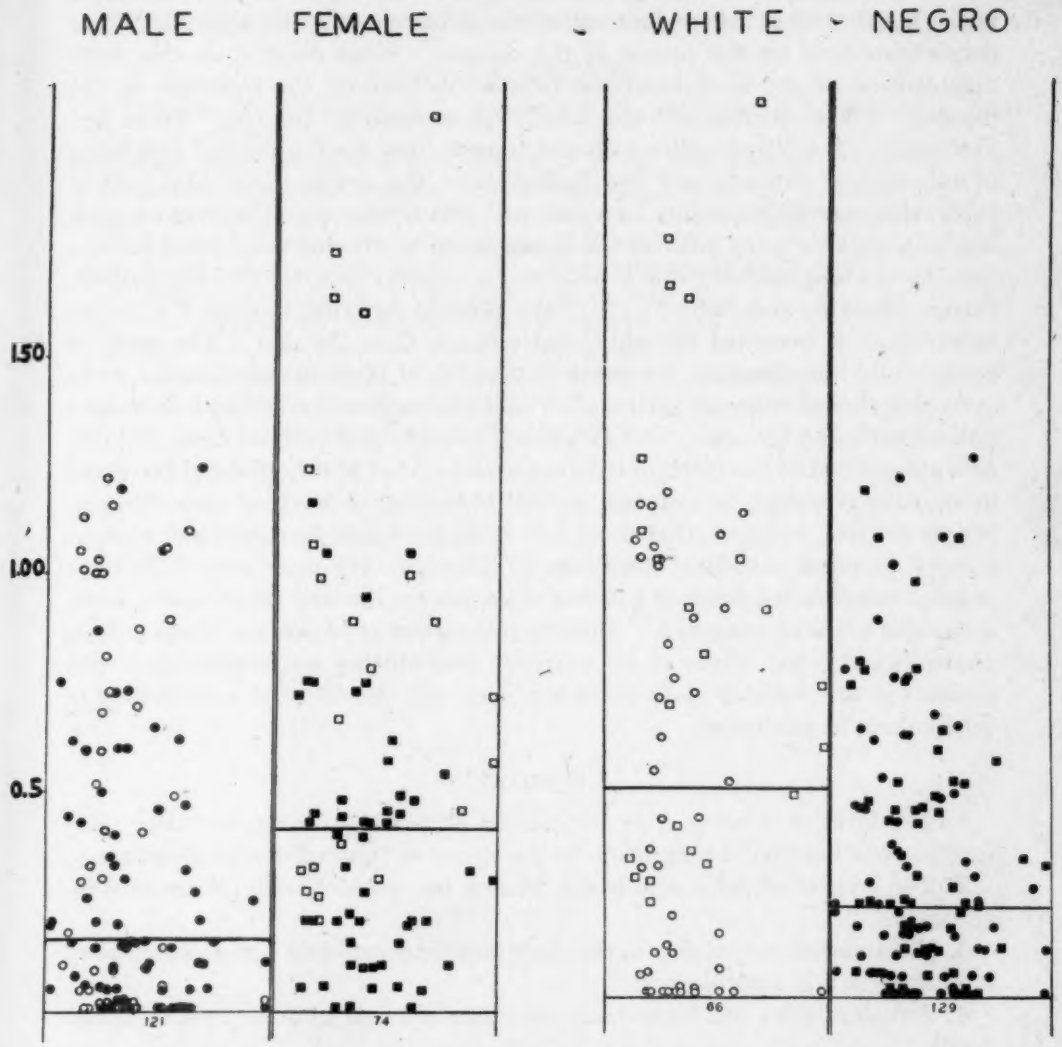

FIG. 4. Plasma vitamin C observations plotted to show the sex and race differences in the nontuberculous patients. In each column of observations the median line divides the observations into halves. This mathematical expression of the average of the observed levels shows the differences in the patient groups.

patients studied in this series had no breakfast before attending clinic and another large group had no citrus fruit for breakfast. Patients who had a citrus fruit breakfast would have higher plasma levels when they were bled in the clinic than they would if they were fasting, but we have ignored this error which

would be in favor of a higher observed plasma level, since our results indicate our subjects are badly malnourished in this respect and the slight additional error is not important.

The following questions are pertinent. What is the significance of vitamin A and C deficiencies in tuberculous patients? What effect would abolishing these deficiencies have on the course of the disease? What effect does this same malnutrition of our nontuberculous population have on the incidence of the disease? These queries are not wholly answerable at present. Years ago McConkey (9) advised codliver oil and tomato juice for the general well being of tuberculous patients and the limitation of the development of intestinal tuberculosis; excellent results have followed this treatment. Codliver oil itself has been used for many years in the treatment of tuberculosis and many institutions have a long standing rule of an ounce of codliver oil a day for each patient. Bogen, Hawkins and Bennett (10) have pointed out that mucous membrane tuberculosis is benefited by additional vitamin C in the diet The work of Sweany and his colleagues (1) shows that length of life is increased and a more favorable clinical response occurs after continued saturation of the tuberculous patient with ascorbic acid. Our data would indicate that vitamin A and ascorbic acid are reduced to low levels in the disease and we feel that both should be given in amounts sufficient to maintain normal physiological levels of each vitamin. We do not feel, however, that these two vitamins should be considered without respect to other nutritive constituents. Sheeley (11) and Levy (12) have pointed out that tuberculous patients often have a lowered prothrombin level, indicating a lack of vitamin K. Only by comparison of patients in whom normal physiological blood levels of all nutritive constituents are maintained, with patients in the depleted state commonly seen, can the effect of malnutrition in tuberculosis be evaluated.

SUMMARY

1. The level of vitamin A in the plasma of recently diagnosed tuberculous patients was lowered in proportion to the extent of tuberculous involvement.

2. The level of ascorbic acid in the plasma was lowered with tuberculous involvement.

3. Nontuberculous patients in the clinic population studied were malnourished in vitamin A and ascorbic acid.

4. Females (white and Negro) had less vitamin A and more ascorbic acid than males.

5. Negroes were more malnourished in both vitamins than were the white subjects.

SUMARIO

1. El tenor de vitamina A en el plasma de los tuberculosos recién diagnosticados disminuyó en proporción a la extensión de la invasión tuberculosa.

2. El tenor de ácido ascórbico en el plasma disminuyó conforme a la invasión tuberculosa.

3. En los no tuberculosos concurrentes a la clínica, que fueron estudiados, también había desnutrición en cuanto a vitamina A y ácido ascórbico.

4. En las mujeres (blancas y negras), había menos vitamina A y más ácido ascórbico que en los varones.

5. Los negros estaban más desnutridos en ambas vitaminas que los blancos.

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THE VALUE OF CODLIVER OIL AND TOMATO JUICE IN THE PREVENTION OF LARYNGEAL TUBERCULOSIS[1, 2]

MACK McCONKEY

The present study deals with the value of codliver oil and tomato juice in the prevention of laryngeal tuberculosis complicating pulmonary tuberculosis. It supplements studies of Smith and myself (1, 2) on the value of the remedy in preventing intestinal tuberculosis. It is generally agreed that during recent years there has been a marked decline in the incidence of laryngeal tuberculosis. Dr. George Wilson, laryngologist in Saranac Lake, informs me that during the last twelve years the number of patients referred to him with laryngeal tuberculosis has steadily declined and at present it is approximately 60 per cent less than in former years. Laryngologists in other parts of the country have noted a similar decline. Some observers hold that this decline may be attributed directly to collapse therapy, which tends to reduce the amount of sputum and free it from tubercle bacilli.

In the present study, therefore, it seemed advisable, in order to determine more precisely the value of codliver oil and tomato juice in the prevention of laryngeal tuberculosis, to exclude those patients who had received any form of collapse therapy. There were 420 patients, 80 per cent in the moderately and 20 per cent in the far advanced stage of pulmonary tuberculosis, who showed no evidence of laryngeal tuberculosis at the time of admission to the sanatorium. The patients in this group did not receive codliver oil and tomato juice, and 14, or 3.3 per cent, developed the complication during their residence at the sanatorium. There were 371 patients, comparable as to the extent of the pulmonary disease, who received the remedy, and only 4, or approximately 1 per cent, developed laryngeal tuberculosis while under our observation. It is to be noted that the patients in these two groups were under exactly the same sanatorium regimen, except for the administration of codliver oil and tomato juice to the latter group. Moreover, for the last fourteen years, the remedy has been used at Ray Brook as a prophylactic measure for laryngeal tuberculosis, and the incidence of the complication arising among our patients has remained at approximately 1 per cent.

Necropsy studies tend to support the value of the remedy in the prevention of laryngeal tuberculosis. In 71 consecutive necropsies at Ray Brook, 41 of the subjects had not received codliver oil and tomato juice during life, and laryngeal tuberculosis was present in 14 instances, or 36 per cent, whereas in 30 subjects who received this remedy during life, laryngeal tuberculosis was found in only 4, or 13 per cent. In other words, the incidence of laryngeal tuberculosis, clinically and at necropsy, was three times greater in the untreated than in the treated

[1] Presented before the Medical Section at the 38th annual meeting of the National Tuberculosis Association, Philadelphia, May 8, 1942.

[2] From the New York State Hospital for Incipient Pulmonary Tuberculosis, Ray Brook, New York.

group. As noted in our autopsies and those of Burke and Aronovitch,[3] the incidence of laryngeal tuberculosis was three times greater in the subjects that also had intestinal tuberculosis.

It is significant that the marked decrease of laryngeal tuberculosis generally noted throughout the country occurred during the fourteen-year period when

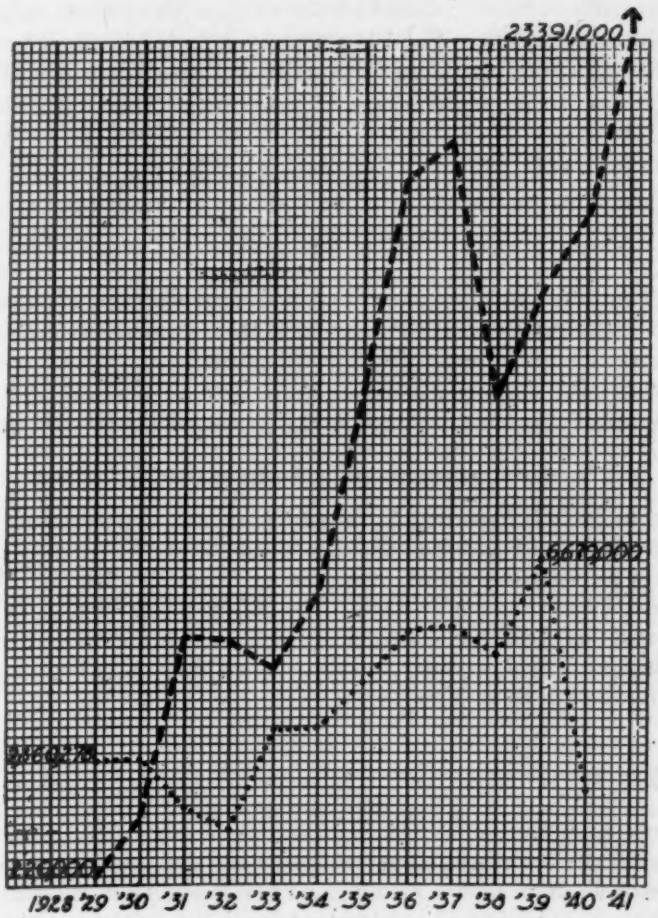

CHART 1. The sale of tomato juice and codliver oil in the United States for the years 1929–1941 inclusive.

---------- Tomato juice—each square represents 200,000 cases.*

..... Codliver oil—each square represents 200,000 gallons.*

* The data were kindly furnished us by the United States Department of Agriculture, Bureau of Agricultural Economics.

there was a hundred-fold increase in the sale of tomato juice in the United States (see chart 1). The increase in the sale of codliver oil was not so striking. This

[3] Personal communication.

may be explained in part by the fact that there are no figures available for the sale of codliver oil derivatives and substitutes.

It appears justifiable to conclude, from the above observations, that the combination of codliver oil and tomato juice is a valuable remedy in the prevention of laryngeal tuberculosis.

At this time it seems advisable, because of the contrary opinions expressed, to amplify briefly our observations on the value of the remedy in the prevention of intestinal tuberculosis. The 774 patients included in the present study had not received any form of collapse therapy; 411 patients in this series in the moderately and far advanced stages of pulmonary tuberculosis did not receive codliver oil and tomato juice and 47, or 11 per cent, developed intestinal tuberculosis during their stay with us. The remaining 363 patients with a comparable amount of pulmonary disease received codliver oil and tomato juice, and only 4, or approximately 1 per cent, developed the complication while at the sanatorium.

During the past fourteen years, the remedy has been used as a prophylactic measure at Ray Brook and the incidence of this complication arising among our patients has remained at approximately 1 per cent.

These observations confirm the previous studies of Smith and myself as to the value of the remedy in the prevention of intestinal tuberculosis (1, 2, 3).

METHOD OF ADMINISTRATION

Attention to detail is important in the administration of the remedy. Three ounces of tomato or citrus-fruit juice are placed in a glass about half the size of an ordinary tumbler. On the surface is placed one-half ounce of plain codliver oil. The "cocktail" is served *ice-cold immediately after meals*. The patient should be told that slight gaseous eructations savoring of codliver oil may be experienced for the first week or so of treatment. In certain instances, it is necessary to substitute codliver oil in ten minim capsules for the usual half-ounce of oil for a week or so.

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DISCUSSION

Dr. M. Maxim Steinbach, New York, New York: The studies of Drs. Getz and Koerner and of Doctor McConkey have greatly contributed to our appreciation of the relationship between nutrition and disease. We are indebted to their exact method and figures. The correlation they have drawn between vitamin A and C deficiency and tuberculous involvement would be a revelation of importance at any time, but is of particular significance at this period in our history. A thorough understanding of this work and an intelligent application of its principles might do much to prevent this country from

suffering the appalling rise in tuberculosis mortality which is the usual trend in times of war.

As has been repeatedly shown, vitamin A deficiency will cause many structural derangements, most important of which is probably the degeneration of epithelium, occurring markedly in the mucous membranes. It has also been demonstrated in experiments in rats that the first damage done by A deficiency is to the respiratory tract. In general, deficiency in man produces the same histological changes as in animals. According to Eddy and Dalldorf, pneumonia and tuberculosis are commonly found associated with A deficiency. Epithelial metaplasia often occurs next to tuberculous lesions, and giant cell formation is noted in the respiratory tract.

Drs. Getz and Koerner have shown that vitamin A deficiency is closely correlated with the incidence of tuberculosis. They report twice as much A deficiency in nontuberculous colored people as in nontuberculous white people. This is extremely interesting in view of the fact that tuberculosis is more than twice as prevalent among the colored as among the whites. To illustrate, in New York City, the colored make up only 6 per cent of the total population, yet they occupy 25 per cent of all available hospital beds for tuberculosis and their death rate is 25 per cent of the total mortality. As is generally known, the colored are also noted for the exudative or invasive form of the disease with very little tendency toward calcification and fibrosis. This coincides with the relationship pointed out by Drs. Getz and Koerner between the percentage of deficiency and the stage of the disease. In our own experience with the administration of codliver oil and tomato juice to far advanced cases of pulmonary tuberculosis with intestinal involvement, we could see some evidence of healing. Doctor Banyai, who has reported strikingly good results with local administration of codliver oil extracts, is convinced that the vitamin A content of the oil is responsible for the healing of the ulcerated membranes.

The studies of Drs. Getz and Koerner indicate that vitamin C depletion was greater than that of A, and again that the deficiency was greater among the colored than among the white.

Their studies of ascorbic acid and the clinical findings of Doctor McConkey are in complete harmony with our findings in tuberculous man and in the experimentally infected animal. In the first place, we agree that the greater the involvement, the lower the ascorbic acid level. In addition, daily injections of ascorbic acid increase the tolerance of tuberculous guinea pigs to repeated large doses of tuberculin. Finally, tuberculous animals treated daily with small doses of ascorbic acid had less tuberculosis, more fibrosis and less caseation than the controls. It is therefore apparent that the loss of vitamin C which occurs in tuberculosis can be compensated with advantage to the patient by additional intake of the vitamin.

In treating intestinal tuberculosis, following the pioneer work of Doctor McConkey, we chose far advanced cases of pulmonary tuberculosis with intestinal involvement and administered crystalline vitamin C daily by parenteral injection. We feel this is a good method to use because the tuberculous gut absorbs materials poorly. In most of the cases there was clinical improvement, with cessation of cramps and diarrhoea, gain in weight, increase in red count, increase in haemoglobin. In some cases of laryngeal tuberculosis there seemed to be definite evidence of healing. We feel that, since all patients with tuberculosis have a serious deficiency of vitamin C, daily replacement by giving tomato juice or citrous fruits, or by the injection of crystalline C, is definitely indicated. This, of course, should be in conjunction with administration of vitamins A and D and other vitamins which may be deficient. It has been found that the tuberculous

individuals are more likely to have reactivation of their disease in winter and early spring, when the average diet is lacking in vitamin-rich fruits and vegetables.

The diet of the general population and of hospital patients has, in the last few years, been greatly improved as regards vitamin content. Therefore it is interesting to find that there has been a slow but steady decline in the incidence of intestinal and laryngeal tuberculosis at the Montefiore Hospital. This lowered incidence is not only a clinical fact but a reduced incidence is indicated from our recent autopsy material. At Bedford Hills, where we keep our early cases, there are at present only 3 cases of clinical intestinal tuberculosis among 230 patients. At Montefiore Hospital, where advanced cases are kept, there are 27 clinical cases of intestinal tuberculosis among 164 patients, or 16.4 per cent. In 1930, there were 38 per cent. At present we have only 31 per cent with clinical and pathological findings of laryngeal tuberculosis. Autopsy studies show that at present 50 per cent of our cases have intestinal tuberculosis (of 207 autopsies reviewed), whereas in 1930, 64.8 per cent showed this involvement at autopsy, and at that time 45 per cent had laryngeal tuberculosis.

The general run of cases, as far as I am able to say, is of the same type as has been admitted in former years. However, collapse therapy is now practiced much earlier and more commonly. The fact that autopsy records also show a reduced incidence of intestinal and laryngeal tuberculosis strongly suggests that the reduction is not altogether the result of collapse therapy, but may be attributed in part, at least, to the vitamin therapy and diet rich in vitamins which many patients took before admission as well as during their period of hospitalization.

Dr. Fred H. Heise, Trudeau, New York: As Doctor McConkey has said, codliver oil and tomato juice do play an important part in the nutrition of the tuberculous. For centuries codliver oil has been used in the treatment of disease and for the past century especially for phthisis or consumption. In 1852 Richard Payne Cotton (1) spoke of it as follows: "Whether we regard this medicine as a means of arresting or of palliating consumption, it undoubtedly ranks higher than any other with which we are acquainted." . . . "The examples of successful employment are so numerous and unquestionable that we have, I think, only to bear in mind the character of the disease we are dealing with, and how utterly powerless against it are the majority of medicinal agents, to be forced to the admission that the use of codliver oil was the commencement of a new and most important era in the treatment of consumption." Much the same was said by John Hughes Bennett (2) (1854) and by Theophilus Thompson (3) (1854). In 1887 C. J. B. Williams (4) stated that in the second ten years of his practice (1840–1850) a marked improvement took place in the results of treatment over the first ten-year period. A purified codliver oil and a liberal diet were prescribed in the second half of the period (1840–1850). Those who took the oil had twice the duration of life as those who did not or who took it irregularly. "Other important constitutional influences succeeded in arresting and curing pulmonary consumption, long before the discovery of the tubercle bacillus and its relation to the disease and we must conclude that they acted by improving the bioplasm and increasing constitutional resistance, thereby enabling the various cells to become the destroyers and not the victims of the bacillus."

In the twenty-five years from 1911 to 1935 many marked modifications in the health, the habits of life and environment of the American people have taken place according to Dublin and Lotka (5), who analyzed the changes in expectancy of life in the Metropolitan Life Insurance industrial policy holders during this period. The public health movement

in America had just gotten under way, medical science learned how to control the most devastating diseases of childhood, surgical methods and methods of diagnosis had vastly improved, the standard of living had far improved as had the conditions under which people worked. Understanding the effect of diet on health, the newer knowledge of nutrition has placed in the hands of the doctor and housekeeper a potent weapon against disease, and many other health promoting changes have taken place. In this period we see the mortality rates per 100,000 for ages one to seventy-four diminish constantly, some tremendously, namely, communicable childhood diseases from 56.3 to 8.7; measles from 11.2 to 2.2; scarlet fever from 12 to 2.8; whooping cough from 7.4 to 1.4; diphtheria from 25.6 to 2.3; tuberculosis all forms from 241.6 to 56.4; tuberculosis of the meninges and central nervous system from 8.9 to 2; tuberculosis of the intestines and peritoneum from 6.7 to 1; tuberculosis of other organs from 5.9 to 1.6, etc. In no part of this period, 1911–1935, had there been a marked decline in the steady trend toward lowering of the death rate for intestinal and peritoneal tuberculosis. At Trudeau Sanatorium the incidence of tuberculous enteritis in moderately and far advanced cases has fallen from 12 per cent of 369 cases in 1924–1925 to 11.7 per cent of 375 cases in 1925–1927 and 8 per cent of 348 cases in 1932–1934; 10 per cent of 358 cases in 1934–1937; 9.5 per cent of 228 cases in 1938–1940 to 6.5 per cent of 183 cases in 1940–1942. At no period has there been a marked drop.

Clinically the change in the pathology of tuberculosis has likewise been noted by those who have treated the disease for many years. Extrapulmonary tuberculosis as a complication of pulmonary tuberculosis has steadily diminished in frequency. Laryngeal tuberculosis has declined from 25.6 per cent in 1914 to 14.6 per cent in 1934 and 3.6 per cent in 1941 in the experience of the late Julius Dworetzky (6) of Otisville. He attributed this decline largely to the use of collapse therapy. However, collapse therapy had not been used on any of the group studied in 1914.

The increased consumption of fruits and vegetables makes it appear that the average person might receive a sufficiency of dietary essentials. Examination of the average diet shows that about one-half of the caloric intake is composed of non-nitrogenous food, such as highly refined sugars and fats, highly milled and processed grain. A small portion of the caloric intake must then supply the necessary proteins, vitamins and minerals. Inadequacy of the dietary essentials and improper choice of foods leads to insufficiency of the essential proteins, vitamins and minerals (7).

Resistance to disease is dependent upon the sum total of all metabolic processes and, because nutritional failure exerts an adverse influence upon metabolic activity, deprivation of one or more essential nutrition factors can readily lead to an impaired immunological response. Vitamins should be looked upon not merely as preventatives of certain pathological states but as substances indispensable for the normal functioning of all tissues of the body, irrespective of their relationship to the frank pathological changes which their deficiency will cause.

Doctor Getz has shown us that many people do not for one reason or another attain normal nutrition in respect to vitamins A and C and that tuberculosis, an infectious disease, does help to further deplete the body contents of these substances. Furthermore, he tells us that after being under treatment the status regarding these two nutritional substances improves. This I take it, may be due to lessened metabolic demands and better food. One significant observation regarding weight and subvitaminosis A and C merits restatement, that is, that nutritional status and weight do not always go hand in hand.

It would seem that the study of nutrition in health and disease is a very complex one

and our knowledge of the facts relating to metabolism, growth and nutrition is very incomplete despite its rapid development. Those who are most intimately associated with the study in an experimental and clinical way impress us with the fact that vitamin deficiencies are seldom single, most often multiple, and that excesses of one may and do upset the balance of others, as happens with ratios of C and D (10) and the components of B complex. For this reason we are admonished to see that we obtain a sufficient amount of the proper quality foods and so prepare them for consumption as to lose little if any of their nutritional values, especially vitamins and minerals, rather than rely upon the commercial products given haphazardly as to dose.

Undernutrition may take place for several reasons (11):

1: Failure to ingest a well balanced diet due to ignorance, limited economic status, social customs, etc.
2: Disturbance of absorption due to nausea, vomiting, diarrhoea; and with certain vitamins, improper intestinal flora.
3: Lack of substances in stomach and intestines which may prevent utilization of vitamins, such as the Castle factor in anaemia.
4: Individual requirements may be higher than usual.
5: Constitutional differences.
6: Increased metabolism due to various causes. An increase in calories, particularly carbohydrates, increases vitamin requirements as do growth, pregnancy, fever, hyperthyroidism, etc.
7: Ingestion of toxic substances.

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TREATMENT OF TUBERCULOSIS OF THE ORAL CAVITY BY CARBON DIOXIDE SNOW

JOSEPH BERBERICH[1]

Tuberculosis of the mucous membrane of the oral cavity is not very common. We see tuberculosis most frequently on the entire mucous membrane of the hard and soft palate, the pharynx, less frequently on the tongue, gum and pillars. Tuberculosis of the mucous membrane may occur as infiltration, as ulcer, as granuloma or tumor (tuberculoma). In most cases tuberculosis of the oral cavity is secondary. That means it is either propagated from the neighborhood or haematogenously or through lymphatic channels. The sputum, which contains tubercle bacilli in so many cases of tuberculosis of the lungs, can sometimes also produce a tuberculosis of the mouth. It seems to me that a primary tuberculosis of the oral cavity is a great rarity.

The symptoms and signs of tuberculosis of the mouth are very characteristic. The different forms of this tuberculosis are characterized by a quick disintegration of the tissue, the chronic course, severe pains independent of chewing and increased by chewing. For this reason it is understandable that the intake of food is very difficult but, on the other hand, we know how important the intake of food is for these patients. Everyone is well aware that we treat tuberculosis by general and local means. Here I will deal only with the local treatment of tuberculosis of the mouth.

Apart from the administration of anodynes we usually use anaesthetic powders which are applied directly to the ulcers. Moreover, we use galvanocautery in different forms; we cauterize with chromic acid, lactic acid, carbolic acid, trichloracetic acid, and finally curettage is done. Other authors recommended irradiation with X-rays, ultraviolet rays, natural or artificial sunlight. Successes are reported with any of these methods. There can be no doubt that these reports are correct. Every experienced physician who has tried all of these well known methods is able to confirm these facts. On the other hand, every physician who has the opportunity to see many of these cases and who is forced to treat such patients might confess that he is not very happy with these methods and that he has to select carefully the proper method of treatment for each case.

I would, therefore, like to draw attention once more to a method which was published more than ten years ago by Nussbaum and Teebrügge. This method was tested by the authors in the same clinic in which I was an associate and I was able to follow-up and use this method for more than seven years. The method to which I refer is the carbon-dioxide-snow treatment of tuberculous affections of the mouth. The same method was used for tuberculosis of the larynx but this point will be excluded from this discussion.

It may be worth noting that we can achieve excellent results in the larynx, too, if we apply with special instruments the carbon-dioxide-snow to the larynx.

[1] 784 Park Avenue, New York, New York.

We always used the indirect method of laryngoscopy because we considered pulmonary tuberculosis as a contraindication to direct examining methods in the larynx or to bronchoscopy. I could imagine that with the direct methods in the larynx or bronchoscopy, as they are widely used in this country in cases of tuberculosis, one could very easily achieve good results (perhaps even better ones than we did) with an application of carbon-dioxide-snow in the larynx.

We found the treatment with carbon-dioxide-snow to be easy. It can be applied with good success primarily in cases with progressive ulcerating tuberculosis of the mouth. Granulations of a tuberculous nature and granulomata in the oral cavity also react well on freezing with carbon-dioxide-snow. On the other hand, chronic proliferative forms with strong proliferation of the connective tissue cannot be influenced to a satisfactory extent. In those cases it is advisable that a curettage be first performed in order to freeze the artificial ulcer at the same session.

The freezing of the diseased tissue must be performed at the first session as intensively as possible; after an interval of two weeks this procedure is repeated and, perhaps after another two weeks' interval, it may be repeated once more. If the defect is not too large two freezing procedures are usually sufficient.

By the snow treatment the tissue becomes firm and white and looks like tissue on the freezing microtome. Some minutes later the tissue looks as it did before the treatment and one cannot see that an intervention had taken place. After two to three days the frozen site shows a hazy coating and around the frozen area we find a hyperaemic zone. The hazy "fur" consists of fibrin. Necrosis does not occur. The treated parts clean very quickly after five to six days and fresh granulations soon appear. After twelve to fourteen days a smooth, fine scar develops. The scar can hardly be differentiated from the healthy surroundings. A relapse is very uncommon, no cicatricial contraction or distortion and no defect formations are observed. This treatment itself is absolutely painless. No precautions are necessary for this therapy and no local or general disadvantages can be observed. Care must be taken only at the epiglottis because of the easy development of oedema.

Technique of treatment: We use the carbon dioxide from the tank which we otherwise use for frozen sections. The carbon dioxide is allowed to flow directly from the tank either into a chamois cloth, a leather bag or into a bag made of oilcloth; the carbon dioxide precipitates in the bag as dry snow. In a china dish the snow which has a temperature of $-57°C.$ is mixed with acetone and stirred with a wooden tongue depressor so that a pulp forms; then the carbon-dioxide-snow which has now a temperature of $-90°C.$, is ready for use. Having anaesthesized, with cocain or pontocaine but without adrenalin, the surface of that part of the tongue or the mucosa which has to be treated, we press the mixture of carbon dioxide and acetone firmly upon the diseased site for five to six seconds. As soon as the frozen part has thawed, that is when the previous color reappears, it is advisable to freeze it immediately once more. By the firm pressure of the snow on the ulcer the action in the depth of the diseased tissue is developed. The pressure on the tissue has to be exerted so firmly that no

gas layer develops between the mucous membrane and the snow (Leidenfrost's phenomenon). After two weeks at the earliest the next treatment is given, as mentioned above.

The application of the carbon-dioxide-snow in the oral cavity is very simple. One fills a paper cigarette-tube with the mixture of carbon-dioxide-snow and acetone and one pushes the ice mixture by means of a small stick, the head of which is wrapped with cotton-wool, from the large opening of the cigarette-tube through the small opening which is pressed against the ulcer. With this procedure we can reach everywhere in the mouth. Instead of a paper cigarette-tube we can use an ivory tube. Tubes of metal are ill suited for this purpose.

From the beginning of these investigations I was able to examine all the histological material which had been taken by biopsy in order to follow the changes in the tissue due to freezing. It is certain that the healing is accomplished by the formation of new granulations and fibrous tissue. Moreover, the healing procedure is very similar to that after cautery.

I had the opportunity to use this therapy in the past seven years in more than 200 cases. It has always been confirmed that this method is superior to other forms of therapy and that it is very simple in its application.

We used this method first of all in tuberculous ulcers of the oral cavity; here the success is very quickly achieved. After two to three treatments the ulcers are usually healed and, amazingly enough, even if the general condition of the patient is very poor and the process in the lungs is progressive and exudative. Two to three days after the first treatment the ulcer looks hazy because of the fibrin exudation on the ulcer; the ulcer itself is surrounded by a pink hyperaemic zone. On the fifth or sixth day the exudate begins to slough off and on the ninth or tenth day the ulcer is filled out by fresh granulations and on the twelfth to fourteenth day a very thin scar, hardly recognizable, covers the former ulcer. If this is not the case, we apply once more carbon-dioxide-snow on the fourteenth day and, after two weeks, for a third time if necessary. We practically never had to treat these ulcers more than three times. Almost all ulcers of the mouth may be cured by this method. We never treated more than two ulcers at the same time. Besides the local improvement in the mouth, this healing exerts a stimulative effect upon the psychic condition of the chronic patient; he becomes coöperative. The pains disappear and the food intake improves, an important factor in the treatment of tuberculous patients.

The second, smaller group of lesions consisted of tuberculous granulations in the oral cavity. They react to snow just as the ulcers. The results are good. About 75 per cent are cured by two to three treatments. The granulations shrink after the first treatment, then they are covered by a fibrin exudation; between the tenth and twelfth day they slough off and after two weeks a thin scar is formed. In these cases, too, more than three treatments were never required.

The third, small group of lesions were granulomata of the mouth. They are less responsive to the treatment. It depends primarily upon the size of the granuloma; if it is not as large as a Lima bean the freezing method works the

same way. However, if it is larger than a Lima bean it is advisable to perform a curettage first in order to remove the granuloma and, immediately after, at the same session, the carbon-dioxide-snow is applied. The further course is the same as with ulcers. Here, as in the other groups, the results were good.

The fourth group contains forms of chronic proliferative tuberculous vegetations. They do not react to snow application. This is due to the presence of copious amounts of fibrous tissue. But if we first do a thorough curettage and apply the snow immediately thereafter, we get some good results but not by far as good as with the other groups.

We did not disregard the general health condition of the patient. In addition to the local treatment the general treatment was continued. However, we tried the snow treatment in almost all cases of oral tuberculosis, even the severest. If we thought that the body of the patient reacted at all, we tried the freezing therapy. To our own surprise we often saw, even in desolate cases, that this method accomplished good local results.

Other authors, such as Eschweiler, Albanus, Wiegand, published good results.

I should like to mention in addition that another simple method can be of great value in cases of tuberculosis with pain and difficulty on swallowing due to ulceration. This is inhalation of lime water.

Lime water (*aqua calcis*) is calcium hydroxide, dissolved in water to about 0.15 per cent; it combines with fatty acids to form insoluble soaps, thus condensing the lipid parts and cement substances of the tissue. Probably the precipitation of calcium carbonate plays a rôle too in covering the tissue mechanically. The low concentration of lime water excludes any caustic action on the tissue, its alkaline quality enables it to dissolve the tenacious mucin adhering to the mucous membranes, thereby aiding the cleaning of the membranes and neutralizing acid fluids.

We ask the patients to inhale lime water three times a day for ten to fifteen minutes. The use of solvents is unnecessary because the inhaled lime water dissolves sufficiently.

The lime water is inhaled through a mask connected with a nebulizer or inhaler driven by oxygen under pressure. Instead of the common inhaler we can interpose between oxygen tank and mask a simple Bergson tube which disperses the lime water to the smallest of particles for inhalation. Even patients with tuberculous ulcers of the larynx find this inhalation a great relief. In patients who suffered only from ulcers of the mucous membranes of the mouth very good results were obtained; namely, quick relief of pain. Sometimes in the beginning of the inhalation therapy the patients complain of increased pain on swallowing because fibrin and pus in the ulcers slough off, the ulcers become clean, thus denuding the nerve endings in the ulcers. Within a few days the ulcers fill up with new granulations which in turn cover the nerve endings again. Usually after six to seven days pain is markedly decreased. Although this method is very old, it was not applied for many decades. We used this therapy during the last seven years routinely in all cases of ulcerative processes in the mouth and throat. It seems to us that lime water inhalation is a great help to

our patients with ulcers of the mouth; it eases the intake of food essentially, a very important factor in the treatment of tuberculous patients.

SUMMARY

It has been pointed out that two methods, other than the more customary methods for the treatment of tuberculosis of the oral cavity, should be used in proper cases. One is the treatment of the tuberculous mucous membrane with carbon-dioxide-snow and the second is the therapy by inhalation of lime water.

Both methods have no disadvantages and no ill effects in the oral cavity.

These methods are easily applied and deserve, therefore, a wider application.

SUMARIO

Ya se ha indicado que, además de los corrientes, en los casos apropiados deben utilizarse dos métodos para el tratamiento de la tuberculosis de la cavidad bucal. Uno de ellos es el tratamiento de la mucosa tuberculosa con nieve de bióxido de carbono, y el segundo es la terapéutica por inhalación de agua de cal.

Ninguno de los dos métodos posee desventajas ni ejerce efectos contraproducentes en la cavidad bucal.

Ambos métodos son de fácil aplicación, y merecen, por lo tanto, que se les utilice más ampliamente.

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TUBERCULOUS MENINGITIS[1]

Its Clinical Features as Observed in a General Hospital

JERRY ZASLOW AND BENJAMIN DICKSTEIN

Our interest in tuberculous meningitis was stimulated by the fact that, from November, 1940 to April, 1941, 6 patients with this disease were admitted to the Jewish Hospital of Philadelphia. We were impressed by the infrequent appearance of the classical textbook picture in the early stages of the disease. It is said to consist of a prodromal period of weight loss, evening fever, digestive disturbances, poor memory, headache and insomnia, lasting several weeks. This is supposed to be followed by the stage of invasion which is characterized by vomiting, headache, constipation and neurological signs and finally by stupor, coma and death (3). Having reviewed all the cases seen here during the past twelve years, it is our purpose to show that this syndrome is not commonly found and to suggest means by which an earlier diagnosis may be established. This is particularly important in a general hospital where tuberculosis in any form is only occasionally encountered and where tuberculous meningitis is not too often seriously considered.

HISTORY AND REVIEW OF LITERATURE

Robert Whyte in 1768 was the first to obtain accurate knowledge of this condition. Guersant in 1828 observed the tubercles in the meninges. Rilliet and Barthez described the symptomatology, as did Gerhard in Philadelphia (3).

Walgreen (11) states, "Tuberculous meningitis is the most fatal of all the diseases of children, and the morbidity and the mortality are identical." Blacklock and Griffin (1) bring forth the fact that tuberculosis is the most common cause of meningitis in children. Of 406 consecutive cases of meningitis of all types, 60 per cent were tuberculous, 16 per cent were pneumococcic, 15 per cent were meningococcic, 4 per cent were influenzal and the remainder were due to other organisms. Segal (9), in reporting 1,522 cases of tuberculous meningitis, states that 57 per cent occur in the first three years of life, 26 per cent in the second three years, and 17 per cent between the ages of six and twelve. Thelander and Baldwin (10) give the highest age incidence in their report as two years, one year next and less as the higher age groups are approached.

The observation that the highest incidence is in the young age groups make speculation between the development of this disease and the development of the primary tuberculous complex interesting. Walgreen (11) claims that tuberculous meningitis develops as a complication of the fresh primary lesion and, as scarring, encapsulation and calcification begin, the danger of this complication is greatly diminished. The tuberculin test becomes positive three to seven weeks after the primary infection. The greatest danger of meningitis, then, is between the fourth and eighth weeks after the appearance of the positive

[1] From the Jewish Hospital, Philadelphia, Pennsylvania.

tuberculin test. After three months have passed, the danger is greatly decreased. These facts may be of great significance in prophylaxis. During the danger period it is important to prevent anything that would activate the tuberculous process by placing the child under general hygienic care, making an early diagnosis and watching particularly those under the age of three. Also, an attempt should be made to prevent certain childhood diseases, such as measles, pertussis and pneumonia, all of which favor dissemination and activation in the already infected child. This is well shown in one case in our series of a child who developed tuberculous meningitis some weeks after pertussis.

An early diagnosis is fraught with difficulty, leading to embarrassing mistakes which, though temporary, are nevertheless serious. It has been confused with poliomyelitis, encephalitis, mumps, benign lymphocytic meningitis and the purulent meningitides. To this we may add from our own series conditions entirely unrelated to the central nervous system.

In the papers surveyed, it was the atypical rather than the typical clinical picture that was emphasized. Although the signs of meningitis do predominate in the picture, they are late. Nuchal rigidity is a common finding; however, it may not be marked and is often not present early. It resembles the rigidity as found in the encephalitides. Emaciation is rather uncommon (Thelander and Baldwin (10)). Chest examination is often negative, although the roentgenogram gives a higher percent of positive findings. Boyd and Baron (2) report retention of urine as an early complaint. They also state that a rise in pulse rate with a fall in temperature is suggestive in children. Most reports give nothing significant about the leucocyte count, although there is usually a slight elevation. The tuberculin test is helpful, but not always so, a negative test being not at all uncommon in the presence of a full-blown case of acute miliary tuberculosis. Mental disturbances are the most common findings reported, often resembling closely delirium tremens. Cabot (8) reports a patient in whom the diagnosis of delirium tremens was maintained until death, with not one of a number of consultants even suggesting the true diagnosis. The mental changes of the avitaminoses have been closely simulated according to some reports.

The laboratory findings are important and the diagnosis is most commonly made on the basis of these. The spinal fluid often confirms the diagnosis, but neither the cell count nor the percentage of lymphocytes is absolutely diagnostic. The range of both is within the same limits as that of many other central nervous system diseases. The average cell count as reported is 250 cells, seldom above 500. The higher the count, the higher is the percentage of polymorphonuclear leucocytes. Smear and culture are often negative, particularly on first examination, but with persistence and care, tubercle bacilli can be found. Hemenway, at the Babies Hospital in New York, found organisms in practically all cases (3). Macgregor and Green (7) in their series show that the ideal method for isolation of tubercle bacilli from spinal fluid is both direct culture and guinea pig inoculation; if direct culture is used, the Löwenstein-Jensen medium is most serviceable; animal inoculation yields a higher percentage of positive results than does direct culture, but takes four to six weeks instead of two to three.

The spinal fluid protein is increased, but not markedly so. The chlorides are one of the most significant of the findings. A chloride value of under 645 mg. per 100 cc. is believed by Alpers to confirm the diagnosis, and it is generally believed to be pathognomonic. The sugar is usually decreased, falling as the severity of the condition increases.

The comparative value of the Levinson and tryptophane tests has been much discussed. Tryptophane bodies are said to be increased in this condition, Aiello and Lichtenberg finding the tryptophane test positive in from 90 to 100 per cent of their cases (6). On the other hand, Tooney, Fulton and Rea (4) found the test negative when it should have been positive and positive when it should have been negative in a sizable number of cases and they concluded that the test is valueless. The Levinson test, however, has given more promising results. Pons and Fletcher (5) found the test positive in 90 per cent of their cases and Guistra (6) in all his cases.

All reports give the course of the average case as rarely over four weeks. It may last only a few days or occasionally persists for seven weeks.

REVIEW OF CASES OF TUBERCULOUS MENINGITIS OBSERVED AT JEWISH HOSPITAL

During the twelve-year period between 1929 and 1941, 16 cases of tuberculous meningitis were observed. There were 6 cases from November, 1940 until April, 1941. The remaining cases were scattered over the preceding years. These are studied according to the following plan: admission diagnosis, age distribution, history of contact and past medical history, symptoms and neurological signs on admission, laboratory data, time interval elapsed before the true diagnosis was established, duration of illness and postmortem findings.

It is interesting to note the variety of admission diagnoses (table 1). In the 16 cases there were 11 different diagnoses, of which 6 were not even neurological. In only one case was the patient admitted with a diagnosis of tuberculous meningitis, and this on the basis of definite neurological signs, in a patient with known active pulmonary tuberculosis. One-half of the cases occurred under the age of four and one-third during the second year of life. Yet, just as many cases occurred in the older age groups (forty to sixty) as in the younger age groups. Only 4 cases had a definite contact history; in 3 of these, on the basis of the history with only slight meningeal signs, the true diagnosis was suspected and proved within twenty-four hours. In some charts no history was recorded or it was very scanty. Only 2 cases had known tuberculous disease. In carefully reviewing the cases, signs and symptoms very suggestive of tuberculous disease were found in 6 others, proven later at postmortem examination to have had tuberculosis. Only 6 cases had fever as a presenting symptom. Five had listlessness and drowsiness, 5 had vomiting and only 4 had headache. Two patients were admitted in coma of rapid onset and 2 others with convulsions not preceded by prodromal symptoms. Only 2 had night sweats and one had weight loss. Five patients had completely negative neurological examinations on admission. One had no neurological examination done because the true nature of the disease was not suspected. Six had nuchal rigidity on admission, and in all it was mild.

Six had pupillary signs, 4 had a Babinski sign, 4 had positive Kernig's sign and only 3 had changes in the deep reflexes.

In 4 cases, the diagnosis was made by the examining physician in the hospital on admission, while the longest time interval for diagnosis was eighteen days. The average was five days. The diagnosis was made on the basis of spinal fluid findings in 7 cases, on the basis of the history in 4, and on the basis of a positive Mantoux test in 2 and was not made until postmortem examination in 4 cases.

Spinal fluid examinations were done in 15 of the 16 cases. It was not done in one case because a neurological syndrome was not suspected. The chlorides

TABLE 1

Admission diagnosis

NEUROLOGICAL	NOT NEUROLOGICAL
1. Meningitis....5	1. Intestinal toxaemia....1
(a) Tuberculous....1	2. Dysentery....1
(b) Not specified....4	3. Gastro-enteritis....1
2. Encephalitis....2	4. Bronchopneumonia....1
3. Acute toxic delirium....1	5. Acute tonsillitis....1
4. Jacksonian convulsions....1	6. Sarcoma of left lung....1
5. Herniation of nucleus pulposus....1	

TABLE 2

Postmortem findings

	NUMBER OF CASES	PER CENT
1. Pulmonary involvement	6	50
2. Mediastinal involvement	3	25
3. Mesenteric involvement	1	8
4. Miliary tuberculosis	10	83
5. Pott's disease	2	16
6. No primary focus	3	25
7. Tubercles (base of brain)	11	91
8. Primary focus:		
Pulmonary	4	33
Mesenteric	1	8

ranged from 520 to 710 mg. per 100 cc. and in only one case was the chloride value consistently over 645 mg. The white cell count ranged from 40 to 540, with 76 per cent to 90 per cent lymphocytes. In 14 cases, smears and cultures were done, yet only 2 smears and one culture were positive. Of 5 guinea pig inoculations done, 3 were positive, one was negative and there is no report on the fifth case. Only 3 spinal fluids had pellicle formation and in these the smears were negative for tubercle bacilli. Both Levinson tests done were positive and the 2 tryptophane tests done were negative.

The course of the disease ranged from four days to four weeks, with an average of twenty-three days. The course in the hospital was usually stormy, all the

patients eventually developing marked neurological signs, lapsing into stupor, then coma and succumbing. Twelve postmortem examinations were done. The findings are summarized in table 2.

COMMENTS AND CONCLUSIONS

The foregoing data bring out several important facts. The variety of admission diagnoses indicates how infrequently a correct diagnosis of tuberculous meningitis is considered in a general hospital. This is in direct contrast to what is found in a tuberculosis institution where the diagnosis is suspected early, since this condition is looked for as a complication.

To expect the disease to attack only the youthful is incorrect. The diagnosis can never be excluded on the basis of age. It occurs in isolated cases in all age groups. No doubt, if much larger series are investigated, as reported in the literature, the highest percentage occurs in the younger age groups, but this fact should not mislead us.

It is interesting that in most of the cases where a history of contact was obtained, the diagnosis was established early. A careful investigation of possible contact was not often made. The importance of this is obvious. We may assume that, had a contact history been established in more cases, more diagnosis would have been made early. We must, therefore, more closely inquire into the family history in all cases with meningeal signs or suggestive symptoms. Only 2 cases had known tuberculous disease. We must not suppose that a previous history of tuberculosis need be present to support the diagnosis, for there may be no previous history and usually there is none.

Tuberculous meningitis is not always an insidious disease. It may be as acute and fulminating as purulent meningitis; 4 of our cases were admitted in coma and convulsions without any prodromal symptoms. The disease, at first, may neither simulate meningitis nor give us any suspicion of tuberculosis. The cardinal features of meningitis, fever, headache and vomiting, were present in only a small number of cases, and even fewer had any symptoms suggestive of tuberculosis, such as cough, night sweats or weight loss. It is well to recall that a neurological examination was not done in one case and that there were no neurological signs in 5 others. This is in contrast to the purulent meningitides where neurological findings are almost always present.

The spinal fluid chlorides, white cell count and lymphocyte count agree with the findings in the literature. However, there was a remarkably low incidence of positive smears, cultures and pellicle formation. The laboratory here is representative of those in most general hospitals, and the errors committed here are probably similar to those in similar institutions. No doubt this small number of positive findings is due either to some fault in the laboratory technique, to an insufficient number of requests for such examinations on the part of the physician, or both. We were impressed by the number of cases where only one request for a smear or culture was made. Unceasing effort should be made in an attempt to isolate the organisms where the examiner suspects tuberculous meningitis. It would be well to follow the teaching of Macgregor and Green,

as previously given, that is, direct culture with the Löwenstein-Jensen medium and guinea pig inoculation. Not enough guinea pig inoculations were done, and of the 5 performed, one was negative. Although it is usually a reliable test, a negative finding must not be looked upon as conclusive, particularly if only one examination is done. One must suspect that the infrequency with which the pellicle formation has been observed has been due to failure to allow a specimen of spinal fluid to stand at least twelve hours. We believe the Levinson test is an extremely valuable diagnostic aid, and that it has not been used with sufficient frequency.

The postmortem findings impressed us by the fact that in only 8 cases was previous tuberculosis present. If such examinations showed only this small number we must suspect that an even smaller one will show physical signs. Miliary tuberculosis was found in 10 of the cases. Macgregor and Green present evidence that can be regarded as suggesting that miliary tuberculosis in their cases took origin from the meningitis, since in each case the former seemed to be of shorter duration than the meningitis, and only the lesions in the central nervous system were active enough to be likely to give rise to heavily infected blood. This point is in direct contrast to the popular conception that the miliary tuberculosis precedes the meningitis and that the former produces the latter.

In summary, we may conclude that in any case of bizarre symptomatology with a history or suspicion of contact, or definite evidence of tuberculous infection, with or without definite neurological signs, repeated spinal taps should be done. The fluid should be diligently studied for chloride content, for tubercle bacilli on smear, culture and guinea pig inoculation and the Levinson test should be used.

SUMMARY

1. A brief review of the literature on tuberculous meningitis is presented.
2. Sixteen cases of tuberculous meningitis observed in the Jewish Hospital of Philadelphia, a general hospital, are analyzed.
3. The infrequent appearance of a typical textbook picture of tuberculous meningitis in its early stages, as seen in a general hospital, is stressed.
4. Important diagnostic criteria to aid in its earlier diagnosis are emphasized.

SUMARIO

1. Preséntase un breve repaso de la literatura sobre meningitis tuberculosa.
2. Analízanse 16 casos de meningitis tuberculosa observados en el Hospital General Hebreo de Filadelfia.
3. Recálcase la rareza con que se observa en el hospital general el típico cuadro de las primeras fases de la meningitis tuberculosa, tal como lo dan las obras de texto.
4. Ofrécense importantes pautas diagnósticas para el diagnóstico temprano.

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THE SCAPHOID SCAPULA IN TUBERCULOSIS[1]

EMIL BOGEN AND ARTHUR ROGERS

The descriptions and illustrations of the human scapula or shoulder blade, as seen in standard anatomical texts, represent its inner or vertebral border as convex. In 1906, during the course of a routine neurological examination, Dr. W. W. Graves, of St. Louis, was struck by the markedly concave appearance of the vertebral borders of the scapulae of a patient and by similar phenomena in other members of the patient's family (1). Graves felt that this concave configuration was a definite variant from the normal and warranted further observations.

The careful examination of thousands of scapulae since then convinced him that the vertebral border extending from the mesial end of the scapular spine to the beginning of inferior angle of the bone might be predominantly convex, straight or concave and that the bones could be grouped accordingly. Graves later grouped the straight, concave and mixed forms together, thus reducing his final classification to a convex and a scaphoid type. The material examined included living and dead patients of all ages and both sexes, various primates and prehistoric skeletons. Individuals from all economic strata and many industries, as well as those suffering from a variety of diseases, were also included, so that these scapular groups were drawn from and represent a complete cross-section of the human race as well as its predecessors (2).

Analysis of the proportion of each type seen at different periods of life showed that, after the second decade was reached, there began a sudden and continued drop in the percentage of concave scapulae seen and a corresponding increase in the convex type until, at the eighth decade, over 80 per cent of the scapulae examined were of the convex type. In groups where some form of constitutional unfitness could be postulated, such as prisoners, inmates of institutions for the feeble-minded, and so forth, a predominance of the concave over the convex types was evident, while in soldiers, old people's homes, honor students, etc. the reverse appeared to be the case (3).

Graves reëxamined a group of individuals over a long period of time during which he failed to find any definite evidence of change from one type to another. However, his method of physical examination, in which the personal equation is undoubtedly a factor, is qualitative rather than quantitative, and it is conceivable that a change of slight magnitude, such as that from slightly convex to straight, or from straight to slightly concave, might escape clinical detection.

Physical examination introduces a personal error and may be influenced by nutrition, a fat muscular border being more apt to be felt as convex, whatever the actual shape of the bone may be. This characteristic of the scapula may be much more accurately determined by means of X-ray examination. The routine chest X-ray films, however, introduces difficulties and sources of error

[1] From Olive View Sanatorium, Olive View, California.

that must be recognized, due to the angle at which the shadow of the scapula is projected onto the film, the distortion from the diverging rays and the superimposition of other shadows.

Of especial interest to us is Graves' finding that patients with tuberculosis show a marked excess of scaphoid type scapulae. This finding was reported on the basis of studies of nearly 4,000 patients in six different institutions, examined by four different workers. Physical examination of 100 patients at Olive View showed the same excess of the scaphoid type that had been found elsewhere, only 23 per cent of these patients having convex scapulae.

Comparison of the routine X-ray films and physical findings in these cases showed a reassuring correlation, with complete agreement in nearly 90 per cent of the cases in which the scapula could be seen in the film. The disagreements were mainly concerned with the straight or borderline groups, only 3 cases showing a change from convex to concave by X-ray, and 2 of these were in overweight women where the physical finding may well have been at fault. Not one case which felt concave appeared convex on the X-ray films. Accordingly, further study was made of X-ray films alone of patients suffering from tuberculosis, as well as a large group of presumably healthy employees for control, for this finding. Altogether, we found 145 convex scapulae in 633 patients, or 23 per cent, and 97 convex scapulae in 219 employees, or 44 per cent.

Although convex scapulae are found less often among our tuberculous patients than among our employees, those patients with convex scapulae who are admitted here have no less disease and no better prognosis than those with scaphoid scapulae.

Our data, however, seem quite convincingly to confirm Graves' assertion that, among tuberculous patients, there are fewer convex scapulae than among normal individuals. Whatever may be the inferences drawn from this fact, the mere mathematical relationship seems established.

From the examination of the progeny of families where as many as five generations were available, and of individuals over a period of twenty years, Graves concluded that the type of scapula was a characteristic determined by the germplasm, that it was passed from parents to progeny according to a definite inheritance pattern, and that, once established in the foetus, it was not changed during the lifetime of the individual by growth or development processes, disease or any other factors. He then drew the following sweeping conclusion: "If we accept as proven that nothing in the life of the individual after his birth can change the scaphoid type, then the age incidence of the scaphoid type of scapula points to the conclusion that many individuals possessing this anomaly are, in the broadest sense, the poorly adaptable, the peculiarly vulnerable, the unduly disease susceptible, the constitutionally inferior, the short-lived individuals of the race."

However, there seem to be discrepancies between the reported statistics and the inference that they are due to greater longevity of the possessors of a convex scapula. Even if recorded deaths occurred only among bearers of concave scapulae, there would still be too many surviving to make up the small percent-

age actually found upon examination of higher age groups. Thus, if as reported, 65 per cent of all scapulae at ten years of age are scaphoid, and all deaths occurred only in this group, a total mortality rate of 40 per cent in the next fifty years (above the actual) would still leave 25 per cent of the original scaphoid group, with the entire remaining 35 per cent convex or more than the reverse proportion actually found by Graves, Kollert, etc.

The assertion that the predominance of convex scapulae in the advanced age group is the result of the dying-off of the bearers of scaphoid types and, therefore, represents a survival factor, is predicated upon the supposition that the shape of the bone does not change during life. This would be an exception to Wolff's law that "The form and architecture of bone corresponds mathematically to the physical demands of external stresses." As Steindler states, "so strongly is bone growth under mechanical influence, that it reflects both in external and inner structure the effects of weight and other mechanical stresses . . . this is much more the case under pathological conditions . . . under disease, trauma or operative interference, the adaptive tendency is strong enough to lead to constant changes in form and structure." Thus bow legs may straighten under the physical stresses of splinting, with absorption at the convexity and apposition of bone at the concavity.

The scapula acts as point of origin or insertion for many muscles, particularly the rhomboids and *levator scapulae* on its vertebral border. The pulls of these and other muscles, as well as changes due to postural abnormalities, myopathies, exercise reflex or disuse atrophy, endocrine or nutritional disturbances, general debility and other pathological states, may play a significant rôle in causing postnatal changes in the shape of the scapula during its development. The fact that convex scapulae appear more frequently in males, in advancing years, in stronger and more favored groups, seems to emphasize the rôle of muscle pull in its production.

Scapular variations may be of great interest and even of clinical value, even though their constitutional or hereditary nature is disproven. The fact that these variations do exist, that certain types are preponderantly present in groups manifesting physical diseases or stigmata of constitutional inferiority should stimulate further investigations of the exact mechanism of its production and the causative factors involved. The diagnostic and prognostic value of the scapular type need not be overemphasized, but may occasionally call our attention to local or constitutional conditions affecting or disclosing the cause of pulmonary disease. When next he pats his patient on the back, the doctor may well note not only the winged scapula of Hippocrates but also the scaphoid shoulder blade of Graves.

SUMMARY

The inner or vertebral border of the human scapula is convex in most anatomical illustrations and in the majority of healthy adults observed by Graves and others. In patients suffering from tuberculosis, an excess incidence of straight or even concave scapular inner borders has been observed. Both

physical examinations and X-ray films of patients and employees at the Olive View Sanatorium have confirmed these observations. The occurrence of such scaphoid scapulae in children and in various subnormal groups has been interpreted by Graves as a sign of constitutional inferiority. An alternative explanation based on Wolff's law interprets this phenomenon as an indirect effect of the disease process.

SUMARIO

En la mayoría de los adultos sanos observados por Graves y otros, así como en casi todas las ilustraciones anatómicas, el borde interno o vertebral del omoplato humano es convexo. En los pacientes que padecen de tuberculosis se han observado con suma frecuencia bordes internos rectos y hasta cóncavos, habiendo confirmado estas observaciones, tanto el examen físico como el de las películas roentgenográficas de pacientes y empleados del Sanatorio Olive View. Graves interpreta como signo de inferioridad orgánica la aparición de dichos omoplatos escafoideos en los niños y en varios grupos subnormales. Otra explicación, basada en la ley de Wolff, interpreta este fenómeno como efecto indirecto del proceso patológico.

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CASE-FINDING IN NEW YORK CITY[1]

H. R. EDWARDS[2]

Case-finding is the major activity of the Department of Health in New York City in the prosecution of its campaign to control tuberculosis. The indicated supervision of a given case, such as treatment in institutions and periodic examination in clinics, is also a vital procedure in the control program but it is secondary to the detection of the case. It is estimated that between 1936 and 1940 there was an annual average of 4,956 deaths from tuberculosis (all forms) in the city and among residents who died outside New York City. At the close of 1940, there were 7,118 individuals in institutions in the city or sanatoria out of town. Thus, the ratio of beds to deaths on the above calculations is estimated at 1.4:1. In consideration of the known overcrowding in institutions in the city and the number of cases at home but in need of some form of institutional care, it is estimated that New York City needs 3,000 additional beds.

As important as adequate beds may be in providing treatment or isolation for the active or infectious case, there is no cause to delay or curtail an aggressive case-finding program. The case-finding program during the past years is responsible in large part for the beds now available and the present deficiency will only be met if there is a demonstrated need for them.

The success of a case-finding program depends as much upon the attitude of the public toward tuberculosis as a communicable disease as it does upon the machines and technicians available to diagnose and supervise the case. Edward Livingston Trudeau, the first president of the National Tuberculosis Association, stated in 1905 that, "Education of the people and, through them, of the State is the first and greatest need in the prevention of tuberculosis." Much progress has been made in this direction during the past thirty-five years, but it is obvious that the job is not finished. A recent Gallup poll indicated that a surprisingly large percentage of people do not appreciate the true cause or the potentialities of the disease. This lack of understanding is well illustrated in the difficulty experienced in most communities in securing complete coöperation in the examination of family contacts to known open cases and to prevail upon public authorities to provide the facilities known to be necessary for supervision of the case.

Therefore, there is ample reason to indicate the need for improvement in and expansion of educational methods to secure greater coöperation from the budget-making bodies and from those known to be exposed, as well as the masses of the population who may be considered as potential cases.

The tuberculosis clinics, mass surveys and the institutions treating cases are potent educational factors but, in and of themselves, they are not sufficient to arouse the desired interest of the public.

[1]Read before the Mississippi Valley Conference on Tuberculosis, Columbus, Ohio, October, 1941.

[2] Director, Bureau of Tuberculosis, New York City Department of Health.

This problem is not to be found only among the lay public. The private practitioner does not fully appreciate his responsibility in detecting tuberculosis among the millions who come to him for medical advice and treatment. It has been difficult to arouse interest among the older physicians, but there is no reason why the medical student, interne and resident physician should not be given better instruction on the importance of tuberculosis and the modern methods for diagnosis. It is encouraging to note that there has been substantial improvement in this direction in recent years.

There is an abundance of evidence to show that the problem of tuberculosis is concentrated in the immediate environment of the open infectious case. Thus, the basic program in case-finding must start with a search for disease among those in close contact with an open case. It is impossible in all instances to find the source of infection for the original case diagnosed within a given family unit. We recognize that there are thousands of cases in various stages of the disease in the general population who are unaware of their condition, yet they may have spread their infection to countless others before symptoms develop that cause them to seek medical advice. This problem is particularly important in large urban communities where congested housing and similar opportunities for close contact exist.

Thus, to the program of contact examination must be added some method of reaching the apparently healthy population that have more than an average opportunity to become infected and later develop the disease.

Diagnosis in the early stage of the disease is most desirable, but diagnosis of every case early or late is vitally important too in the control program.

In New York City case-finding in tuberculosis is a responsibility of the general practitioner, the radiologist, private clinical laboratories, hospitals, certain private agencies doing social welfare work and the Departments of Health and Hospitals through established clinics and out-patient departments. All of the foregoing agencies are required by law to report any case of tuberculosis, pulmonary or other forms, to the Department of Health. The registration and responsibility of seeing that cases are properly supervised rests with the Department of Health. Supervision of cases by the practitioner or other private agencies is permitted, providing they meet the requirements of the Sanitary Code, which requires proper isolation of the case and examination of contacts.

Approximately 25 per cent of cases on the roster, classified as active pulmonary tuberculosis, are under the supervision of the private practitioner and there has been a steady increase in this number over the past few years. Undoubtedly, this increase in supervision indicates a greater interest in tuberculosis by the family physician, yet it is obvious that he is not assuming his just share of responsibility in case-finding, considering the numbers of patients under his care for various causes. Too frequently he is not alert to the latent possibilities of tuberculosis and few have at hand the X-ray equipment which is so important in the diagnosis of the disease.

The major facilities for diagnosis and supervision of cases in New York City are to be found in clinics and hospitals. The city is served by 29 district tubercu-

losis clinics, 23 of which are operated by the Department of Health, 4 by the Department of Hospitals and 2 by private hospitals. These clinics are known as official services which are free to the public within specified areas which cover the entire city. In addition, there are 15 other clinics that operate in connection with other hospitals that render for the most part a low-pay service and do considerable ambulatory pneumothorax treatment. They are not districted. In actual volume of services the Department of Health clinics provide approximately 75 per cent of all the diagnostic clinic services in the city.

It may be of interest to indicate the extent of our case-finding activities over the past seven years (1933–1940), as they involve approximately 10 per cent of the present population of New York City.

There has been a steady increase in the admission of cases in our routine district diagnostic clinics in the above period. For the entire period, 388,766 individuals were examined and 32,598, or 8.4 per cent, were classified as significant cases of chronic pulmonary tuberculosis. Our tabulation of clinic activities in recent years shows all cases diagnosed as well as those who are entirely new so far as the Department's roster of cases is concerned. Prior to that the reports showed all cases as newly diagnosed, even though a certain percentage may have been reported previously from other sources. Reliable estimates indicate that this type of duplication is about 35 per cent. Thus, the 32,598 cases reported above should be reduced by that amount to arrive at an approximate number of completely new cases diagnosed in these clinics for the period. That figure would be 21,089, or 5.6 per cent.

In the consultation services for private physicians operated by the Department during the same period of time, 78,070 persons were examined and 10,448, or 13.3 per cent, were diagnosed as having active pulmonary tuberculosis. The percentage of duplication in these services is negligible. The percentage of tuberculosis found in the first year that these services were operated (1927) was 33.3. As the years have passed the percentage of diagnoses has decreased considerably and for the past few years has remained more or less constant. It is reasonable to assume that the practitioner referring cases for consultation is becoming more alert to the possibilities of the disease, irrespective of history, symptoms or physical findings, and is, therefore, depending more upon the radiograph to make his diagnosis.

The mass surveys of apparently healthy adults were started in 1933 and, at the close of 1940, 330,923 persons had been examined with 5,802, or 1.8 per cent, showing evidence of clinically significant pulmonary tuberculosis.

Thus, in a period of eight years the Department of Health has examined 797,759 persons and has found approximately 37,339, or 5 per cent, new cases with evidence of clinically significant tuberculosis. On December 31, 1940 the roster of known cases with pulmonary tuberculosis listed 48,387 of which 19,841 were considered as clinically significant and under some form of medical supervision, and 28,541 were considered as having arrested lesions, an accumulation of the previous six years.

If we apply the Framingham formula of 9 active and 9 arrested cases for each

annual death averaged over the past five years, it will be seen that we do not know the whereabouts of 24,763, or 55 per cent, of the active and 16,063, or 35 per cent, of the arrested cases that are presumed to exist in the community. The Framingham studies were based on physical examination which is now considered inadequate to diagnose all manifest lesions, especially those in the presymptomatic stage of development. Thus, with all our emphasis on case-finding we fall far short of our estimated goal which clearly indicates the importance of expansion in this field.

The examination of contacts to known cases is a basic procedure in the Department's case-finding program. This is a first demand on the district diagnostic clinic, a logical step in the consultation services for physicians and is one of the end results of the mass survey program. However, in the district diagnostic and consultation clinics an increasing amount of attention is being devoted to the routine of X-raying of apparently healthy adults from selected population groups. For example, in the Kips Bay-Yorkville district, in 1940 a coöperative program was developed with the district office of the Department of Welfare to X-ray relief clients above fifteen years of age. A total of 3,429 persons were radiographed at the clinic, which represents 62 per cent of the registered population on relief in that area. There were 98, or 2.8 per cent, of those radiographed who had clinically significant lesions of pulmonary tuberculosis. When it is realized that there are estimated to be 300,000 persons above fifteen years of age on relief in the city, it is obvious that a program designed to radiograph the entire number would be expected to reveal approximately 8,400 new cases, or more than one-third of the estimated unknown active cases.

The organization of such a program presents many difficulties and would add considerable expense in X-ray work, as well as personnel. However, it is a goal toward which we are now directing our efforts. The first problem to be solved has been to make greater use of existing clinic facilities. Therefore, attention has been given to the efficiency of existing procedures used in these services. If the clinic case-load now carried can be reduced without loss of effectiveness in contact supervision, more of the existing facilities will be available for the survey of apparently healthy susceptible groups.

Analyses have therefore been made of the cases under supervision in the clinic with the result that certain changes could be made that would eliminate unproductive routine and focus the major emphasis on the significant and important case. These changes have resulted in a saving of approximately 6,000 man-hours of labor per year, and subsequent analyses give no evidence that through the changes important cases are being missed. Some of the major changes in procedure will be briefly outlined.

Previously each new case admitted had the regulation history form completed, was given a physical examination, children were tuberculin tested using 0.1 and 1.0 mg. Old Tuberculin by the Mantoux method. Reactors were X-rayed and all adults above fifteen years were radiographed. Experience has indicated that in this routine work rarely over 5 to 10 per cent ever show sufficient findings to demand further supervision. The new procedure replaces the regular history

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with a 5 x 8 inch card which gives ample space for contact history and the recording of any presenting symptoms. Each case is seen briefly by a physician and, unless his condition or symptoms warrant complete examination, which is rare, he is sent directly to the X-ray department. If the radiogram is negative, further examination is not done unless the individual is above ten years of age and has had recent exposure to an open case. Those with suspicious or manifest evidence of disease by radiograph are called back to the clinic for complete history, physical examination, etc., and are supervised according to their individual needs.

Those between three and ten years of age with normal X-ray findings are not routinely supervised until they reach the age of ten and then in accordance with their continued exposure to a bacillary case.

The definition of a contact in our practice refers to all persons of whatever age living with or in association with an active case of tuberculosis within the past two years. For purposes of supervision we have divided this group into contacts and possible source cases. A contact in our definition is one who may develop tuberculosis because of exposure and as a rule represents persons below thirty years of age. A possible source case is one from whom infection may be spread to others and as a rule represents those thirty years or older. In our supervision of these two groups, more attention will be paid to the contact case regardless of evident disease by radiograph than to the possible source case having a normal roentgenogram. In fact, the latter group is not supervised further if the X-ray film is normal. Of course, these rules are not applied arbitrarily. The clinic physician is always entitled to the exercise of his best judgment in a given case.

The application of the foregoing principles of supervision have resulted in the reduction of the case-load carried in all clinics which permits more attention to the important cases and to greater use of the clinic facilities in reaching others. In 1940 there was an increase of 18.6 per cent in new admissions and a decrease of 13.2 per cent in the number of visits for medical advice in the clinics, and 12.3 per cent in the visits for other than physicians' service. These changes have resulted in improved morale on the part of the staff as well as greater satisfaction on the part of the patient.

The case-load of Department clinics on December 31 was 16,685 and approximately 60 per cent were classified as contacts without manifest disease. In other words, a considerable amount of time and facilities are being devoted to a group of persons in whom we expect disease to develop. Some recent analyses of contact cases in our clinics have indicated that about two-thirds of the cases to be found will be diagnosed at the time of the first examination following the discovery of the original case, and that within two years from that date the majority will have been diagnosed. Other studies on this point are now being made and, if they reveal the same findings, it will be reasonable to conclude that, providing the source case is removed, it will be unnecessary to supervise contacts with negative roentgenograms beyond two years from the time of breaking the contact.

The best that can be hoped for in the supervision of contacts is that the disease

will be detected in the earliest stages. Certainly there is no reason to hope that the periodic examination in and of itself will prevent the development of a lesion. In fact, experience in the routine supervision of contacts, or possible source cases, indicates time and again that the lesion develops rapidly within a period of a few weeks or months. The frequency of development of these lesions, however, is greater in the contact and in the adolescent and young adult age groups than among the possible source case group. Furthermore, our experience teaches that only a small percentage of contacts will later develop the disease.

The most important step in tuberculosis control is to locate the case whether it is latent or active so that further spread can be controlled. Thus, in a community with wide-spread infection and thousands of potential and active cases undiscovered, it may be advisable to direct all efforts to the routine X-raying of contacts and known susceptible persons and supervising only those with suspicious or manifest lesions.

The mass survey, as a method of case-finding, has been developed according to well conceived ideas based on the curves of the plotted mortality and morbidity. The problem of tuberculosis is more prevalent in tenement house areas and among the unemployed than among those of better social or economic surroundings. The major problem in tuberculosis in New York City is to be found among the colored population. Surveys conducted thus far have shown consistently more tuberculous disease among the colored under twenty-five years of age than among the white population of similar economic level, whereas, the reverse has been true above that age.

Regardless of these findings the mass survey of the colored of all ages is indicated in our opinion. The adult population is of much greater importance in case-finding than are surveys among school children.

In a recent report (1) on 162,446 persons representing fifteen population groups surveyed in New York City, information was presented that clearly indicated the prevalence of tuberculosis by age, color, sex and economic groupings.

The lowest yield was one significant case per 1,000 in a high school and the highest yield was 54 per 1,000 in homeless and non-settled males in New York City. Obviously, the yield per dollar invested varied in a like proportion.

The Department of Health extended its mass case-finding facilities to the U. S. Army (2) in November, 1940 at the time of the first call for men to be inducted into the Army. Up until January, 1941 we assumed full responsibility for personnel and X-ray examinations. At that time the Army took over the contract for X-ray service and on January 15 appointed qualified clinicians from the Reserve Corps to read the films. From the beginning of the draft this Department has been responsible for the follow-up of all resident men who were rejected at the Induction Centres for this area. This has given us an opportunity to follow each case and see that proper supervision is provided. A small percentage of such cases on complete study have been adjudged satisfactory for military service. The local draft boards have worked very closely with us in this program. If a man fails to report after the induction board examination, a letter to the chairman of the board results in the issuance of an order to the delinquent to

appear. It is of interest to point out that it has only been in the first three corps areas of the United States Army (Maine to Virginia) that a radiographic examination has been provided for all inductees from the start.

Thus, in conclusion, case-finding is the basis of tuberculosis control, and irrespective of available beds should be increased in any community where the disease still remains a problem. It is of the utmost importance that these programs be expanded at this time. There are thousands of men and women now returning to jobs in industry after months or years of inactivity. Many have had latent lesions that have remained dormant mainly because the individual has had a somewhat sheltered existence, even though he may have been on relief. The sudden return to regular work, requiring a steady expenditure of physical energy, may be just enough to cause a relapse. The increased income incident to employment opens opportunities for recreational activities not previously enjoyed, and this fact, plus the regular work of the job, may be responsible for the breaking down of an imperfectly healed tuberculosis.

To-day considerable attention is being directed to national defense in America, and one of the most serious problems confronting the administrator of public health is the control of tuberculosis. It is one of the important communicable diseases that invariably increased during periods of war. The safest defense, so far as tuberculosis is concerned, is to find the cases now and get them under supervision so that there will be less opportunity for advanced disease to develop and, thereby, less chance for the further spread of infection to others.

In this campaign we need not alone physicians, nurses and machines, but an increased interest in tuberculosis by the public as well. Health education in the past has been responsible for much of the present favorable situation in regard to tuberculosis. However, the job is not finished and greater effort must be made to secure the whole-hearted coöperation of the laity to utilize existing facilities to the end that tuberculosis may be completely eradicated.

SUMMARY

Case-finding is the basis of tuberculosis control in the program of the New York City Department of Health. Three major efforts in case-finding have been presented. Through these sources, 799,659 persons were examined between 1933–1940 with the result that 37,339, or 5 per cent, were found to have significant lesions.

In order to speed up our program, many of the previously standardized procedures were greatly simplified, permitting greater emphasis on the important contacts and cases rather than to scatter our efforts equally among all patients admitted, a large majority of whom are in no practical need of intensive supervision. The mass survey principle has been applied to the district clinic.

It is the policy of the Department to intensify its case-finding program regardless of the availability of beds for all cases discovered.

There is an indicated need for more mass education of the public about the facts of tuberculosis. The undergraduate medical student and nurse need more education in this field, and the practicing physician, if thoroughly interested, could contribute more in the control program than is the experience at this time.

SUMARIO

El descubrimiento de casos constituye la base de las obras antituberculosas del Departamento de Sanidad de la Ciudad de Nueva York, y descríbense tres grandes esfuerzos en este sentido, por virtud de los cuales se reconoció a 799,659 personas entre 1933–1940, descubriéndose 37,339 (5 por ciento) con lesiones importantes.

A fin de acelerar el programa, se simplificaron considerablemente muchos de los procedimientos previamente normalizados, lo cual permitió concentrar más la atención en los contactos y casos importantes, en vez de esparcir los esfuerzos por igual entre todos los enfermos recibidos, muchos de los cuales no necesitan en realidad una vigilancia intensa. El principio de los catastros colectivos ha sido aplicado en las clínicas de distrito.

El Departamento se propone intensificar el descubrimiento de casos sin preocuparse de si hay camas disponibles para todos los enfermos descubiertos.

Parece aparente la necesidad de una educación más general del público en los hechos relativos a la tuberculosis. Los estudiantes de medicina y de enfermería necesitan más enseñanza en este punto, y el médico, si se interesara como procede, podría contribuir más a la lucha que lo que ha hecho hasta ahora.

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TUBERCULOSIS IN THE HOUSEHOLD[1, 2]

Its Occurrence in Marital Partners and Other Members of the Household when the Primary Case Was a Parent or Another Member of the Family

RICHARD G. HAHN

In a recent publication (1) it was shown that 8.3 per cent of persons exposed to clinical (manifest) tuberculosis in the household subsequently developed clinical disease; that an additional 7.1 per cent had asymptomatic (latent) lesions of the adult (reinfection) type and 0.63 per cent had asymptomatic lesions of the first infection (childhood) type, making a total of 16.0 per cent that had developed either asymptomatic or clinical disease. The latent lesions were recognized by radiographic examination only, for they had not caused symptoms or physical signs of disease.

The same material was utilized in this report. The households were divided into three groups according to the relationship of the primary case (first person known to introduce clinical tuberculosis into the family) to the household. In the great majority of the families the primary case was the husband or father, the mother or wife, or in a few instances one of the children. In a very small group of families the primary case was some other relative, a boarder or roomer, but these were so few in number that the families were not included in the final analysis. The population of the households, arranged according to the relationship of the primary case to the family, is given in table 1.

No distinction was made between primary cases whose sputum contained tubercle bacilli and those whose sputum was not known to contain tubercle bacilli (sputum negative or unknown). The latter group was very small compared with the former, and it was felt that the great majority of persons with clinical tuberculosis eliminated tubercle bacilli at some time during the course of their illness. In view of these circumstances it seemed reasonable to consider them as one group.

There were 229 families (table 1) in which the husband (father) was the primary case, 113 in which the wife (mother) and 72 in which a son or daughter (sibling) introduced tuberculosis into the household. This gave a group of 414 families and a corresponding number of primary cases with 1,495 persons exposed to the disease, or a total population, including the primary cases, of 1,909.

All persons exposed to the disease were recorded for one to five years inclusive, following the beginning of their exposure. A single diagnosis, either no disease, asymptomatic tuberculosis, or clinical tuberculosis, was made at the close of the period covered by their record. Any individual who had more than one diagnosis during this period, for example, first asymptomatic disease and later clinical tuberculosis, was given the more serious diagnosis as the final one. Thus the

[1] From The Pulmonary Clinic of the New York Hospital.

[2] Studies and observations included in this paper were aided by a grant from the International Health Division of The Rockefeller Foundation.

report is equivalent to a "follow-up" of persons exposed to tuberculosis in the household for a period of one to five years after the beginning of their exposure.

The diagnosis of clinical tuberculosis was made either as a result of the examination in the clinic or from reliable evidence furnished by the family, a physician or another institution. The diagnosis of asymptomatic (latent) disease could be made only if the examination included a roentgenogram of the chest. All contacts who were not examined in the clinic, or who attended the clinic but failed to have a roentgenographic examination, were recorded as unexamined. A contact was listed as examined if he or she had had one or more roentgenographic examinations of the chest. Among the contacts who were examined were quite a number whose roentgenograms showed a lesion without any accompanying symptoms or physical signs of disease. These lesions (asymptomatic or latent tuberculosis, early minimal, or even occasionally moderately advanced disease without symptoms or physical signs of disease) varied considerably in their radiographic appearance depending largely on the age of the person.

TABLE 1

Population of the households and the relationship of the primary case to the family

PRIMARY CASE	MEMBERS OF THE FAMILY			NUMBER OF PERSONS IN HOUSEHOLD	
	Husbands (fathers)	Wives (mothers)	Other members of family	Including primary cases	Contacts only
A. Husband (father)	229*	229	511	969	740
B. Wife (mother)	113	113*	264	490	377
C. Son or daughter (sibling)	72	72	306**	450	378
Total	414	414	1,081	1,909	1,495

* Primary cases.

** Includes 72 primary cases.

Some represented soft infiltrations apparently of recent origin, especially among persons fourteen to thirty years of age, while others looked like healed or healing processes with dense fibrous strands and were usually found in the older persons. These lesions had remained asymptomatic (latent), but in many instances it was impossible to state whether the lesion was dangerous or significant without rather prolonged observation including serial roentgenographic examinations. The registration of these lesions was considered important because they were often the forerunners of clinical (manifest) disease, especially among adolescents and young adults, and epidemiologically, because they furnished evidence of the contagiousness of tuberculosis.

The percentage of those found to have asymptomatic lesions in the examined group was applied to the unexamined contacts, and the number thus estimated to have asymptomatic lesions plus the number actually found by examination gave the total number with these lesions. This number divided by the total number of contacts gave the final percentage with asymptomatic lesions.

Table 2 shows the distribution of the population according to the relationship to the family of the primary case with the number and percentage that developed clinical and asymptomatic disease during one to five years following the beginning of exposure.

TABLE 2

Primary case with relationship to the persons exposed in the household: The number and per cent who developed clinical and asymptomatic tuberculosis during one to five years following the beginning of their exposure

CONTACTS IN HOUSEHOLD	NUMBER EXPOSED	DEVELOPED CLINICAL TUBERCULOSIS		NO CLINICAL TUBERCULOSIS					TOTAL WITH ASYMPTOMATIC DISEASE, OBSERVED AND ESTIMATED		PER CENT OF ALL EXPOSED PERSONS WITH CLINICAL OR ASYMPTOMATIC TUBERCULOSIS
				Examined by X-ray			Unexamined				
		Number	Per cent	Total	Asymptomatic lesions observed		Total	Number estimated with asymptomatic disease	Number	Per cent of all exposed persons	
					Number	Per cent					
Primary case, husband (father)											
Wives	229	18	7.9	100	13	13.0	111	14	27	11.8	19.7 ±2.63
Children											
*0–9	323	7	2.2	130	7	5.4	186	10	17	5.3	7.4 ±1.46
*10+	188	11	5.9	94	3	3.2	83	3	6	3.2	9.0 ±2.09
Primary case, wife (mother)											
Husbands	113	6	5.3	57	11	19.3	50	10	21	18.6	23.9 ±4.01
Children											
*0–9	176	9	5.1	78	3	3.8	89	3	6	3.4	8.5 ±2.10
*10+	88	5	5.7	45	3	6.7	38	3	6	6.8	12.5 ±3.53
Primary case, son or daughter (sibling)											
Mothers	72	3	4.2	38	3	7.9	31	2	5	6.9	11.1 ±3.70
Fathers	72	3	4.2	34	3	8.8	35	3	6	8.3	12.5 ±3.90
Children											
*0–9	61			31			30				
*10+	173	10	5.8	114	6	5.3	49	3	9	5.2	11.0 ±2.38
Total	1,495	72	4.8	721	52	7.2	702	51	103	6.9	11.7 ±0.83

* Age at beginning of exposure.

Regardless of the relationship of the primary case to the family, the percentages of consorts and of children, ten years of age and older when their exposure was initiated, who developed clinical tuberculosis were practically the same. The highest percentage, 7.9 per cent, was found among the wives of husbands with clinical disease; and the lowest, 4.2 per cent, among parents in families where a son or daughter was the source of the infection in the household. Among children zero to nine years of age at the beginning of exposure, the highest

percentage, 5.1, with clinical disease was found in households where the mother was the primary case, as compared with 2.2 per cent where the father was the source of infection. In households where the primary case was a sibling, none of the children in the zero to nine year age group had either clinical or asymptomatic disease. However, since there were only 61 children in the group, the figures probably merit only this passing remark.

The picture is changed considerably when the frequency of asymptomatic lesions is considered. These furnish additional evidence of the contagiousness of the disease and its spread among those exposed to it, just as the Wassermann reaction reveals the presence of syphilis, even though the usual clinical signs and symptoms are not apparent. Examinations, including roentgenograms of the chest, of the wives and husbands of partners with clinical tuberculosis revealed that 13.0 and 19.3 per cent respectively had asymptomatic lesions of the adult (reinfection) type. Applying these percentages to the unexamined group gave 14 and 10 persons, respectively, among them who probably had similar lesions. Adding these to the number found on examination gave a total of 27 and 21, or a final percentage of wives 11.8 and husbands 18.6 of tuberculous consorts who had asymptomatic lesions. These figures were considerably higher than those found among other contacts in the household. Combining the percentages of asymptomatic and clinical disease gave 19.7 and 23.9 per cent of the wives and husbands respectively of consorts with clinical tuberculosis who had either symptomatic or clinical disease, approximately one and a half to three times as much as any of the other contacts in the household.

These percentages are both higher than those for mothers or fathers in households in which the primary case was a son or daughter, although the difference is more significant statistically among husbands (fathers) exposed to tuberculous wives as compared with fathers exposed to tuberculous siblings, than the difference between wives (mothers) similarly exposed. It should be noted that it was the high incidence of asymptomatic lesions among husbands and wives, particularly the former, that made the difference so striking.

Table 3 shows the figures for marital tuberculosis reported from Philadelphia (2) and those found in New York.

A considerably higher percentage of the wives and husbands exposed to partners with clinical tuberculosis in Philadelphia (2) was found to have asymptomatic and clinical disease than was found in New York: 30.3 per cent and 41.5 per cent compared to 19.7 per cent and 23.9 per cent, respectively. The percentages for either clinical or asymptomatic disease were uniformly higher in Philadelphia than in New York, although the difference was more conspicuous in the percentages of those with asymptomatic lesions.

During recent years roentgenographic surveys have been conducted among large groups of people both as a case-finding measure and to discover tuberculosis early in its development. The percentage of persons in these groups found to have tuberculosis furnishes some measure of the incidence of tuberculosis at large as contrasted with the incidence among the family groups of this report. The data from these large surveys is obviously not strictly comparable to that

of the households which were subject to observation over a period of years and embraced persons of all ages. Nevertheless, with these objections in mind a limited comparison was made.

Edwards *et al.* have reported (3) that among 28,331 members of labor unions in New York, with an average age of 32.2 years, there were 3.9 per cent who had lesions that were classified as "chronic pulmonary tuberculosis," which included lesions that were regarded as arrested. The incidence of clinical and asymptomatic disease among marital partners of persons with clinical tuberculosis in

TABLE 3

Clinical and asymptomatic tuberculosis in consorts of partners with clinical disease in Philadelphia and New York

	NUMBER EXPOSED	DEVELOPED CLINICAL DISEASE		EXAMINED BY X-RAY			UNEXAMINED		TOTAL ASYMPTOMATIC DISEASE		PERCENTAGE WITH ASYMPTOMATIC AND CLINICAL DISEASE
					Asymptomatic disease			Number estimated with asymptomatic disease			
		Number	Per cent	Number	Number	Per cent	Number		Number	Per cent	
*Philadelphia											
Wives exposed to husbands with clinical tuberculosis	234	22	9.4	134	31	23.1	78	18	49	20.9	30.3 ±3.01
Husband exposed to wives with clinical tuberculosis	142	15	10.6	43	15	34.9	84	29	44	30.9	41.5 ±4.14
New York											
Wives exposed to husbands with clinical tuberculosis	229	18	7.9	100	13	13.0	111	14	27	11.8	19.7 ±2.63
Husbands exposed to wives with clinical tuberculosis	113	6	5.3	57	11	19.3	50	10	21	18.6	23.9 ±4.01

* Figures combined for consorts exposed to partners with tuberculosis with tubercle bacilli and with no tubercle bacilli in the sputum.

New York and also among other contacts in the household was considerably higher than that found among the members of labor unions.

The examinations of applicants for employment with the Metropolitan Life Insurance Company and of employees of this company, reported by Reid (4, 5), revealed that among the former 2.1 per cent was the highest annual incidence of pulmonary tuberculosis from 1928 to 1939, and among the latter 0.6 per cent was the highest from 1930 to 1939. These rates are exceeded ten to thirty-five times by the incidence of asymptomatic and clinical tuberculosis found among the consorts of partners with clinical disease in New York. The applicants for employment were made up largely of females and well over half of them were

in the age group seventeen to twenty-nine years, an age and sex in which the incidence of the disease is usually high.

The figures given by Reid for employees (5) may be grouped on a five-year basis, making them somewhat more comparable to those of the households. They show that, during 1930–1934 inclusive, out of an average annual number of 13,427 employees, there was a total of 305 persons with tuberculosis ("all cases"), giving an incidence of 2.27 per cent with tuberculosis during this period. Similarly, during 1935–1939 there was 1.18 per cent with tuberculosis.

It is interesting to note in Reid's report that only 6.4 per cent of the persons with tuberculosis found among the applicants for employment, and among employees only 3.0 per cent of those with "clinically significant" lesions, gave a family history which led to their detection.

Reports by Spector from St. Louis (6) and Paterson from Philadelphia (7) state that tuberculosis among consorts of partners with the disease (clinical tuberculosis) is considerably higher than is found in the general population. Each of them approached the problem differently, the former using the data from the files of the Tuberculosis Division of the St. Louis Health Department, and the latter using material assembled at the clinic of the Henry Phipps Institute in Philadelphia.

DISCUSSION

The figures presented in table 2 demonstrated that there was a considerably higher incidence of clinical and asymptomatic (latent) tuberculosis among the marital consorts of partners with clinical disease than among the other contacts in the household, which no doubt is a reflection of the close association that prevails among marital partners. The difference was most conspicuous in the incidences of asymptomatic lesions which, with the exception of children less than ten years of age at the beginning of exposure, were lesions of the adult (reinfection) type. The percentages of consorts of tuberculous partners who had clinical and asymptomatic disease in New York were considerably lower than those reported by Opie and McPhedran (table 3) from Philadelphia (2). The difference existed largely in the percentages of asymptomatic lesions, especially among husbands exposed to wives with clinical disease. Probably the longer period of observation in Philadelphia accounted for some part of the higher incidence found in that city, for the maximum period of observation there was eight years following the beginning of exposure as compared with five years in New York. Also, it should be noted that in Philadelphia a relatively small number of the husbands exposed to wives with clinical disease were examined, and this may have had some bearing on the high percentage, 30.9, with asymptomatic tuberculosis.

A limited comparison was made of the results found in New York households and those of a mass survey among 28,331 members of labor unions (3) in New York. The survey among members of the labor unions revealed that 3.9 per cent had chronic pulmonary tuberculosis, although only 0.6 per cent were regarded as "clinically significant". The diagnosis of chronic pulmonary tubercu-

losis is approximately equivalent to the combined diagnosis of clinical and asymptomatic lesions. The rate of clinical and asymptomatic tuberculosis among consorts of persons with clinical disease was five to six times higher than the percentage found to have chronic pulmonary tuberculosis in the labor unions. It was interesting to note, similarly, that the incidence of the disease among other contacts in the household who were ten years of age or older when their exposure was initiated was approximately two to three times greater than that reported from the survey of the labor unions.

The difference between the incidence of tuberculosis among applicants for employment with the Metropolitan Life Insurance Company, employees of this company, and persons exposed in the household was even greater, although, again, only a limited comparison could be made. Among the applicants, over a period of twelve years, the highest annual rate was 2.1 per cent, and among employees, over two periods of five years each, 1930–1934 and 1935–1939, the cumulative rates were 2.27 and 1.18, respectively. These rates are exceeded approximately ten times by the incidence of clinical and asymptomatic tuberculosis found among the consorts of partners with clinical disease in New York.

It seems reasonable to infer from these figures, regardless of minor differences in nomenclature and the fact that the data from labor unions and the Metropolitan Life Insurance Company were not entirely comparable with those of the household study, that there is a considerably higher rate or frequency of tuberculosis among persons exposed in the household than among the general population. The difference was most conspicuous when comparisons were restricted to the consorts of tuberculous persons, although the other contacts in the household had uniformly higher rates than were found among the members of labor unions and the applicants for employment with, and employees of, the Metropolitan Life Insurance Company. It also seems reasonable to infer that intimate association is an important factor in the transmission of the disease and that these lesions of the reinfection type are for the most part exogenous in origin.

The registration of tuberculous lesions, particularly of the adult (reinfection) type, is important epidemiologically even though they may be regarded as arrested or healed, or always may have been asymptomatic. They signify that the exposure has been sufficient to produce disease. These asymptomatic lesions follow various courses. Some remain asymptomatic and unchanged in their roentgenographic appearance for periods varying from months to years, while others progress to clinical disease a few weeks or months after their discovery. The former course is more apt to be followed by asymptomatic lesions discovered in persons of the older age groups, and the latter course in adolescents and young adults.

One of the characteristics of tuberculous disease is that lesions may remain dormant for years or progress so slowly that the individual is unaware of any change subjectively. There are few better reasons for urgently advising periodic health examinations, at least annually, than the discovery of a tuberculous lesion, even though preliminary study fails to reveal any evidence that the lesion is active.

SUMMARY

Data have been presented giving the results of the examinations of members of households in New York City over a maximum period of five years following the beginning of their exposure to tuberculosis in the family. In the households in which the primary case was one of the parents, the marital partners of the primary cases had a higher incidence of tuberculosis than any other group of contacts; but in households in which the primary case was a son or daughter, the parents had practically the same incidence of the disease as the other members of the family with the exception of infants and very young children. Households in which the primary case was a sibling serve as a control group for those in which one of the parents was the primary case, emphasizing that marital consorts of partners with tuberculosis have the greater risk of contracting the disease, no doubt due to their close association with each other.

Data also were presented showing that the incidence of tuberculosis among persons exposed to the disease in the household was uniformly higher—two or more times—than that reported from a survey of members of labor unions (3) and from the examination of applicants to, and employees of, the Metropolitan Life Insurance Company (4, 5). The labor and Metropolitan Life Insurance groups furnished an index of the amount of tuberculosis found by radiographic examination among a large number of adults.

Comparison with a similar study carried out in Philadelphia some years ago showed that marital consorts of partners with the disease in Philadelphia had a higher incidence of clinical and asymptomatic disease than was found in New York. The longer period of observation in Philadelphia accounts in part for this difference.

CONCLUSIONS

1. Marital consorts of partners with tuberculosis have a higher incidence of the disease than other members of the household.
2. Intimate contact or exposure, such as occurs in households, is accompanied by a higher incidence of the disease than that found in large groups where the exposure is more casual.
3. Lesions of the adult (reinfection) type are exogenous in origin.

CONCLUSIONES

1. En la ciudad de Nueva York, la frecuencia de la tuberculosis es bastante mayor entre los miembros de hogares expuestos a tuberculosis en la familia, y en particular entre los esposos de tuberculosos, que la comunicada tras el examen de un gran número de miembros de uniones obreras de la ciudad y de solicitantes y empleados de la Cía. Metropolitan de Seguros de Vida.
2. El contacto o la exposición íntima, tal como se observa en el hogar, acompáñase de una frecuencia mayor de la enfermedad que la observada en grupos numerosos en que la exposición es más fortuita.
3. Las lesiones de tipo adulto (reinfección) son de origen exógeno.

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FOLLOW-UP OF THE KNOWN TUBERCULOUS PATIENT[1,2]

KATHARINE R. GUEST

In the sixty years since Koch proved the infectious nature of tuberculosis there has been a continuation and acceleration of the downward trend in tuberculosis mortality which had manifested itself first about the middle of the eighteenth century (1). Meanwhile, bovine tuberculosis has all but been eradicated in the United States. The reduction in incidence of tuberculosis in cattle from 10 per cent in 1908 to 0.7 per cent in 1936 (5) is a convincing demonstration of the efficacy of controlling tuberculosis through controlling the source of infection. This study is an effort to ascertain what means are employed toward a similar end in the control of human tuberculosis in Philadelphia.

Since it is known that tuberculosis is a relapsing disease and that certain cases are not amenable to therapeutic measures for sputum conversion, it appeared to us that the simplest control measure would be adequate supervision of the known case. Therefore, with a view to analyzing factors involved in relapse and death, it was decided to study the follow-up of a group of patients discharged after having had sufficient symptoms or signs to have warranted sanatorium care.

METHOD

A list of patients discharged to Philadelphia from the three Pennsylvania State Sanatoria in 1935 was compiled from sanatorium lists on file at the State capital, Harrisburg. Of the 470 patients discharged from Cresson, Hamburg and Mont Alto in 1935, 143 were ruled out for the following reasons: 41 had died at or within a month of discharge, making them obviously unsuited for this study; 22 were nontuberculous; 1 had left before a diagnosis had been established; 79 had no listing at the Philadelphia Division of Tuberculosis. A group of 327 was the final number suitable for study.

Records available in Philadelphia were analyzed for the seven years 1935–1941 inclusive, at the Division of Tuberculosis, its thirteen City Chest Clinics, and at eight non-City chest clinics. Verbal reports were obtained from private physicians.

The form used was the one adopted by the National Tuberculosis Association in a study of 6,906 patients discharged from public institutions (2). It is quite similar to one used in the study of 4,450 tuberculous patients discharged from Wisconsin sanatoria (7).

In this study relapse is considered to mean readmission to a sanatorium or hospital for tuberculosis, medical advice to be so readmitted, X-ray evidence of activity, or haemoptysis attributed to tuberculosis.

[1] From the Department of Preventive Medicine, Woman's Medical College of Pennsylvania, Philadelphia.

[2] Condensed from a portion of a thesis submitted as a requirement for receiving the degree of M.D.

MATERIAL

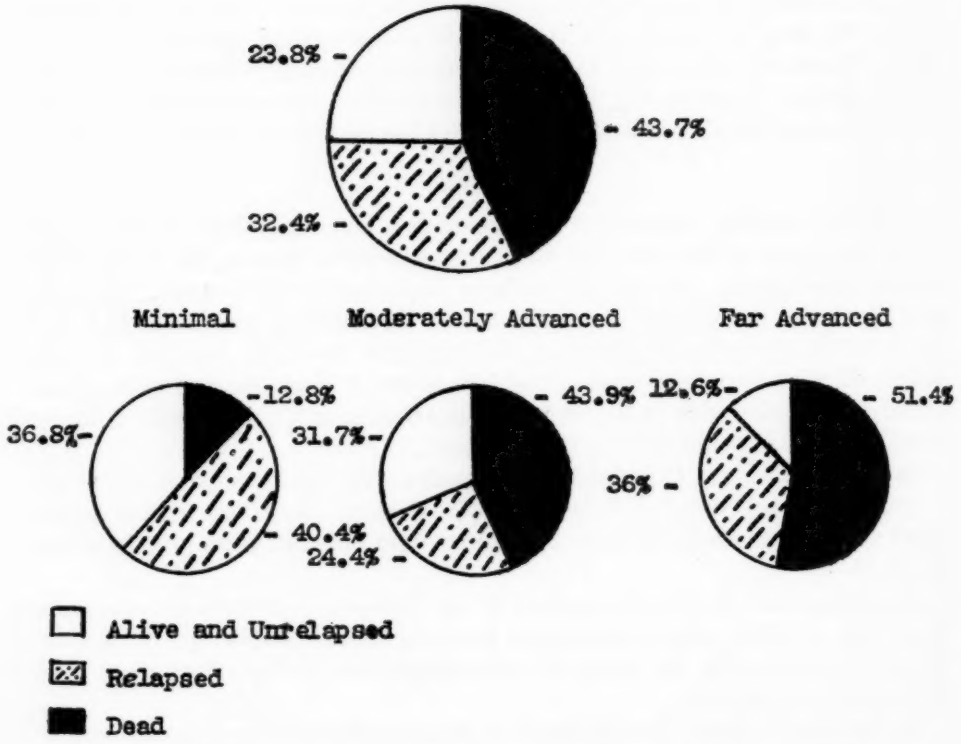
Of the group of 327 known tuberculous patients studied, the status of 105, or 32.1 per cent, is unknown for at least one year prior to January 1, 1942. Chart 1 shows the fate of the remaining 222 cases.

In the ideally handled Stephens (6) Metropolitan group, 1.5 per cent of minimal cases had died five years after discharge, as contrasted to our 12.8 per

CHART 1

222 PATIENTS WHOSE PRESENT STATUS IS KNOWN

Fate 7 years after sanatorium discharge



cent seven years after discharge; 20.7 per cent of moderately advanced cases, compared to our 42.6 per cent; and 46.9 per cent of far advanced cases compared with our 52.5 per cent. Apparently, the fate of far advanced cases differed little despite superior care. However, treatment and follow-up supervision appeared increasingly important the less the involvement.

Our percentage of 32.1 per cent whose present status is unknown is far too

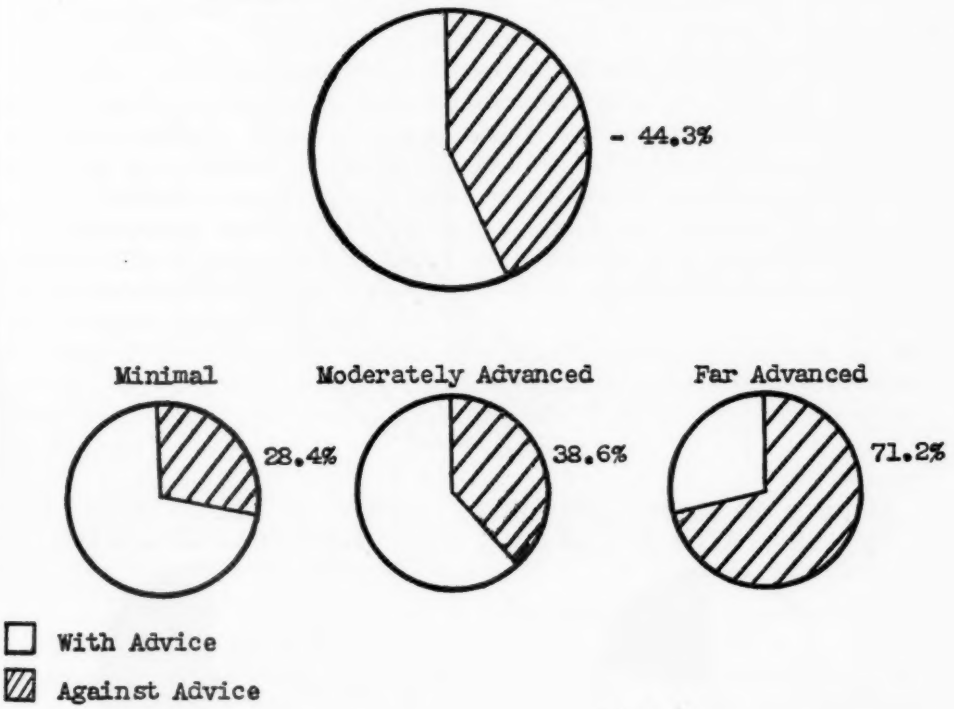
high, but it includes, in addition to 31, or 9.5 per cent, who actually could not be located, a group who had not been seen by a physician either since discharge or from one to six years prior to January 1, 1942.

Hastings and Doerr (4), in a ten-year follow-up study on 1,072 cases from Glenn Lake Sanatorium, found the average stay 1.1 years. In our study, the stay varied from one day to 2,245 days with a median of 173.2 days (approximately five months and two weeks).

Length of sanatorium stay and subsequent relapse or death could not be correlated, even when stage of disease and reasons for leaving the sanatorium

CHART 2

REASONS WHY 327 PATIENTS LEFT THE SANATORIA



were considered. The brevity of all stays may have obscured the relationship one would logically expect to find.

Chart 2 is conclusive evidence of the public health menace presented by the patient allowed to direct his own case.

Dismissal for poor conduct is not the method of choice for solving disciplinary problems. Such patients are precisely the types who will be thoroughly uncooperative regarding care of sputum. They must not be turned from our sanatorium doors while in an infectious state. Eighteen patients in our group were dismissed for poor conduct, 9 of whom were classified as far advanced and 4

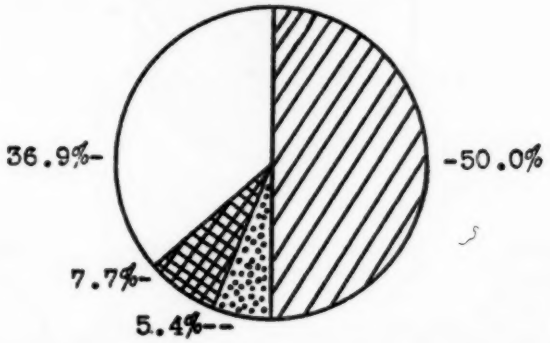
TABLE 1

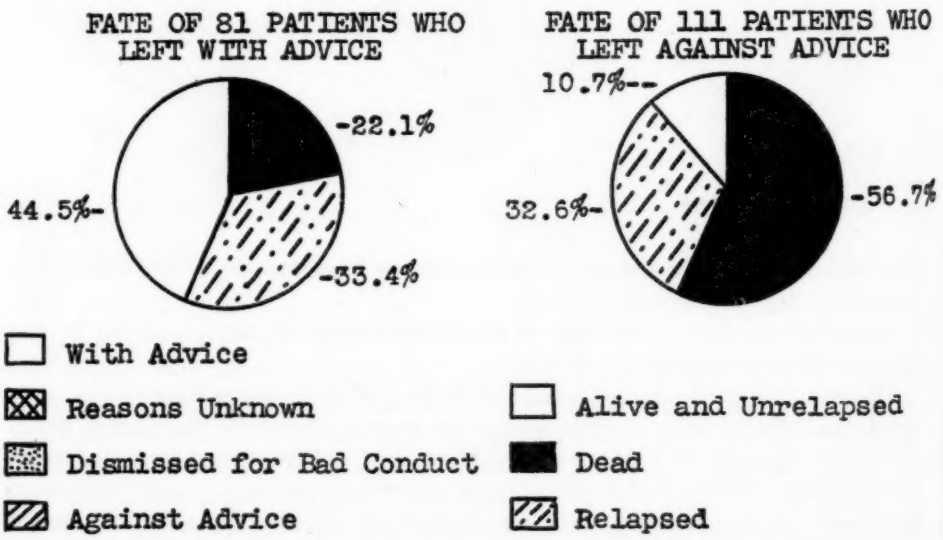
327 patients classified according to fate and to number having had post-discharge clinic visits, X-ray films, and sputum examinations

FATE	NUMBER OF PATIENTS	AT LEAST 1 CLINIC VISIT		AT LEAST 1 X-RAY FILM OR FLUOROSCOPIC EXAMINATION		AT LEAST 1 SPUTUM EXAMINATION	
		Number	*Per cent*	*Number*	*Per cent*	*Number*	*Per cent*
Alive, well	53	50	94.3	37	69.8	32	60.4
Relapsed	72	63	90.3	52	72.4	44	61.1
Dead	97	49	50.5	16	16.5	26	26.8
Status unknown	105	65	61.9	14	13.3	14	13.3
Totals	327	229	70.0	119	36.4	116	35.5

CHART 3

REASONS WHY 222 PATIENTS WHOSE PRESENT STATUS IS KNOWN LEFT SANATORIUM





as moderately advanced. It is interesting to note that, of these 18 cases, 5 are known to have relapsed, 5 to have died, while the fate of 6 is unknown.

Information on sanatorium discharge cards was insufficient for study of relationships of sputum status and stated work capacity on discharge to subsequent fate. No correlation was found between stated condition on discharge and subsequent fate.

In patients who were X-rayed subsequent to discharge, the median interval between the last X-ray examination and last clinic visit was approximately six months. Of all discharged patients, 30 per cent never came to a clinic and 63.6 per cent of those that did report to a clinic were not X-rayed. Sputum studies could have been made even on patients who never came to a clinic. Yet 64.5 per cent of the patients in this study never had a sputum examination following discharge. The commonest cause for this neglect seems to be the patient's statement that he has no expectoration. This statement should not be accepted without investigation. The patient should be carefully instructed in the collection of sputum. In the presence of 3 negative specimens by concentration methods, 3 gastric washings should be required. It is inconsistent to set up, as a criterion for discharge of Philadelphia patients undergoing compulsory isolation, a minimum of 3 negative sputa and 3 negative gastric specimens when other patients' word for lack of sputum is accepted. We do not hesitate to do considerable laboratory work in the control of typhoid fever. It will be necessary to do considerable work if we are to relegate tuberculosis to the present status of typhoid fever.

Of 327 patients, 97, or 29.8 per cent, were removed from the active file by city nurses. Only 2 of these were closed out because the diagnosis was revised. The balance were closed out for the following reasons, many of which are obviously inadequate:

Well and working	1
Unable to locate	31
No reason given	4
Refuse to return to clinic	8
In sanatorium	7
Moved into city	1
Attending private physician	42
No longer under supervision by Catholic Bureau	1
	95

Of the 42 cases allegedly under the care of private physicians, 6 records gave no physician's name, one listed a chiropractor, 2 physicians' names were not listed in the current telephone book, 2 physicians are in the army and one is doing graduate work and their patients' records are not available, 2 are connected with mental institutions and one with a prison outside the city. The following information was obtained from talking with the remaining 27 physicians:

I. *Cases not followed:*

5 cases unknown to physicians named
4 cases not seen by physicians named for at least five years
3 cases not seen by physicians named since discharge

II. *Cases inadequately followed due to poor medical supervision:*

5 cases, stated to be inactive, had no sputum or X-ray examination since discharge from the sanatorium

III. *Cases inadequately followed due to lack of coöperation of patient:*

1 case seen once, one year ago, sputum and X-ray studies advised; patient never returned, check-up revealed that patient was not at address given
1 case advised to have thoracoplasty February, 1941, not heard from since
1 case advised to return to bed-rest November, 1940, refused, continued working, has not been heard from for six months

IV. *Cases adequately followed:*

1 case died following three subsequent sanatorium stays
4 cases receiving pneumothorax or pneumoperitoneum (2 still positive)
1 case died of tuberculosis

In addition to instruction given, of what value is the home visit? It is difficult to set up criteria by which to judge this matter. At the present time the decision as to which homes shall be visited is up to the individual nurse. Visits are frequently made to homes where such supervision is unimportant while other cases in urgent need of home visits are neglected. Random examples of this are taken by sampling our collected data: 4 minimal cases without subsequent symptomatology had 148 home visits during seven years in addition to 87 visits they made to a clinic during this period. Only one of these was a contact case. In contrast, 4 cases discharged as far advanced, all of whom died in from ten months to two years after discharge, had follow-up examinations as follows: one had neither clinic nor home visits; one made two clinic visits, but had no home visit; one made no clinic visit, but had one home visit; and the last had five home visits in addition to his three clinic visits.

An individual nurse consulted about an individual case can usually give detailed information. However, the nursing notes leave a great deal to be desired. The most frequent entries are "visited," or "doing nicely," which do not convey information as to whether or not the patient was seen. Objective information is almost entirely absent. Subjective information is frequently unreliable, as evidenced by an entry of "well and working" shortly before death, or an entry of "failing rapidly" followed shortly by "well and working." There is urgent need for adoption of a standardized form which would convey objective information.

RECOMMENDATIONS

Ideally, a municipal sanatorium under Division direction should be established to provide liaison between active therapeusis and postsanatorium follow-up along with closer proximity to family and friends. In recognition of the value of graduated exercise and of the knowledge that beyond bed-rest lies vocational training and an opportunity to earn, a municipal sheltered workshop should be established. Once the capital costs were met, such a project should be self-supporting through work like community and municipal printing, stamp-making, etc. Patients could be kept at part-time work until placed in suitable

positions or in educational institutions outside. From both a business and a public health point of view this would be far preferable as a protection to money invested in the treatment of these patients than is relief, or the far too frequent method of turning the patient loose economically so that he often hides his tuberculosis and takes the first job he can get, suitable or unsuitable. The patient permanently unsuited for rehabilitation could be kept permanently at part- or full-time work under surveillance and supervision.

The passage of legislation necessary for compulsory examination of contacts, suspects and known tuberculous patients would greatly facilitate the management of the uncoöperative patient. Legal machinery for compulsory isolation of these patients is already available and in use.

Pending adoption and completion of this ideal program, the following suggestions are offered as being immediately practicable:

I. *Pertaining to the sanatorium:*

1. Criteria for admission should be standardized.
2. Since the tendency to leave against advice diminishes with increased length of stay, concerted effort should be directed immediately after admission and for the next three to six months toward educating the patient to understand his disease and the value of sanatorium treatment.
3. The patient at the sanatorium should not be lost track of. Sanatorium reports should be sent to the Division at stated intervals. Prior to discharge, at least one week's notice should be sent to the appropriate clinic so that a check-up can be made on the address to which the patient states he will return. This would reduce the number of patients lost immediately following discharge. A Division nurse or social service worker should be assigned to part- or full-time duty at the sanatoria to visit Philadelphia patients to ascertain their social, psychological and economic problems and to relay these to Division nurses. This would greatly help in promoting contentment and relaxation during cure.
4. Discharge information should be standardized.
5. No patient requiring treatment should be dismissed for poor conduct. He should be transferred to the Municipal Hospital.
6. The Division should send follow-up information on patients to the sanatoria at stated intervals to enable medical staffs in sanatoria to correlate their treatment with the patient's status after discharge. Only thus can the ability to prescribe exercise and to gauge work-capacity be perfected.

II. *Pertaining to postsanatorium follow-up methods:*

1. Criteria should be set up for the frequency at which patients should be visited in the home and should attend clinic and for stated minimal intervals at which X-ray and sputum examinations should be made.
2. The coöperative patient should have the same standards of negative sputum applied to him as are applied to the uncoöperative patient undergoing compulsory isolation. Cultural methods in sputum examination should be used.

3. Supervision of nurses should be provided in accordance with the standards set up by the National Organization of Public Health Nurses, which include one supervisor to every eight field nurses.
4. Standardization of nursing reports should be arranged, placing in writing the objective findings, such as temperature, pulse, respirations, character of work, wages, dates when work was begun and completed, etc., which will lend themselves to future analysis.
5. No case should be closed for a non-medical reason by the individual nurse at the clinic. Such cases should be reviewed by a supervisor to make certain that nothing further can be done to follow them.
6. Notification of suitable authorities in institutions, counties, and cities should be made when patients under care of the Division leave Philadelphia jurisdiction.

III. *Pertaining to local physicians and private agencies:*

1. Non-city clinics and private physicians undertaking the treatment of tuberculous patients should be legally required to follow such patients at stated intervals and in the precise manner regarding X-ray and sputum studies to be prescribed for the City Chest Clinics. Information about these patients should be sent to the Division at stated intervals and the Division should be notified immediately if the patients do not coöperate.
2. Effort should be continued toward education of the local physicians so that greater coöperation is obtained from them in the earlier diagnosis and reporting of cases.

CONCLUSIONS

1. The follow-up care of the known tuberculous patient discharged from the three Pennsylvania State Sanatoria to Philadelphia in 1935 was seriously inadequate. It was characterized by wide variations dependent on the individual clinical and nursing staff, by lack of criteria and coördination, faulty clerical methods, and insufficient study by X-ray, sputum examination and tuberculin test.

2. Length of sanatorium stay was not found to bear a direct relationship to subsequent relapse and death. A possible explanation may lie in the short median stay of five months and two weeks.

3. Departure from the sanatorium against advice is a problem of the first magnitude, both from the viewpoint of the patient's prognosis and public health. Of the 222 patients in this study whose present status is known, 50 per cent left against advice. Only one out of 10 in this group of 111 uncoöperative patients remained alive and well seven years after discharge, while over half of them died and 33 per cent relapsed. The tendency to leave against advice increased with increased gravity of the tuberculosis, as evidenced by the fact that 71 per cent of all far advanced cases, 39 per cent of moderately advanced cases and 28 per cent of minimal cases left against advice. Of all cases leaving against advice, 58 per cent were far advanced and 20 per cent were moderately advanced.

CONCLUSIONES

1. El cuidado subsecuente de tuberculosos conocidos trasladados en 1935, de tres Sanatorios del Estado de Pennsylvania a Filadelfia, resultó muy inadecuado, caracterizándose por amplias variaciones impuestas por el personal clínico y enfermeril, falta de buen criterio y de coordinación, organización defectuosa de las oficinas, e insuficientes estudios roentgenológicos, exámenes de esputo y tuberculinorreacciones.

2. La duración de la estancia en el sanatorio no guardó relación directa con la recaída o defunción subsecuentes. La explicación quizás radique en la breve estancia media de 5 meses y dos semanas.

3. La salida del sanatorio a pesar del consejo del médico, constituye un problema de primera magnitud, tanto desde el punto de vista del pronóstico del paciente como de la salud pública. De los 22 pacientes que comprende este estudio y cuyo estado actual se conoce, 50 por ciento abandonaron el sanatorio a pesar del consejo del médico. Sólo 1 de 10 de este grupo de 111 enfermos que se rehusaron a cooperar estaba vivo y gozaba de buena salud a los siete años del alta, mientras que más de la mitad habían muerto y 33 por ciento habían recaído. La tendencia a abandonar el sanatorio contra el consejo del médico guarda relación con la gravedad de la tuberculosis, según demuestra el hecho de que 71 por ciento de todos los casos muy avanzados, 39 por ciento de los moderadamente avanzados, y 28 por ciento de los mínimos abandonaron el sanatorio contra el consejo del médico. De todos los casos que abandonaron el sanatorio a pesar de dicho consejo, 58 por ciento estaban muy avanzados y 20 por ciento moderadamente avanzados.

ACKNOWLEDGMENTS

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THE EPIDEMIOLOGY OF TUBERCULOSIS IN A LOW-INCOME GROUP[1,2]

RAYMOND E. MILLER AND BEATRICE HENDERSON

Within recent years, due primarily to the development of rapid and inexpensive methods of X-raying large numbers of people, the survey method of tuberculosis case-finding has been used with increasing frequency. This technique has not only proven effective in locating many cases of previously unsuspected disease, but it has also increased our knowledge of the prevalence of tuberculosis in various population groups, depending upon their age, sex, race and economic level. The information thus gained has enabled workers to concentrate surveys on those groups where tuberculosis has been found to be most prevalent.

An equal amount of information is not available, however, concerning the development of new tuberculosis in persons whose original survey X-ray film has been negative; nor are many data available concerning the future course of those whose X-ray films show tuberculosis of the reinfection type which appears to be healed, or whose activity cannot be immediately determined. Additional knowledge concerning these factors would aid in planning case-finding programs, based upon the survey method.

Studies which have been reported on the results of periodic chest X-ray examinations have been carried out among groups of three types: medical students, nurses, internes and other hospital personnel (1, 2, 3, 4, 5); inmates of mental institutions (6, 7); and groups employed in various industries (8, 9, 10, 11).

It has been pointed out that the first group has more exposure to tuberculosis than the general population and, therefore, may be expected to show a higher incidence of this disease. The second group is thought to be more prone to tuberculosis because of overcrowding and factors of poor personal hygiene (12, 13). Certain of the employed groups studied, such as hard rock miners (9), have a special industrial hazard.

The only studies which, to our knowledge, have been reported on population groups without a special risk of tuberculosis are those of Fellowes (8) and Reid (11) on workers at the Home Office of the Metropolitan Life Insurance Company, and those of Sawyer (10) at the Eastman Kodak Company. The former have reported that the incidence rate of new tuberculosis dropped from 7 per 1,000 per year in 1928 to 1 per 1,000 per year in 1939. Sawyer found that the tuberculosis morbidity rates declined from 2.08 to 0.47 cases per 1,000 per year between 1923 and 1939.

So far as we know, no studies of periodic reëxaminations for tuberculosis have been reported on groups of very low income level, although such groups have repeatedly been shown to contain a comparatively high percentage of tuberculous persons (14). Moreover, no studies of this nature have been reported on

[1] From the Tuberculosis Clinic of the Kips Bay-Yorkville Health Center of the New York City Department of Health, and the Department of Public Health, Cornell Medical College, New York City.

[2] Aided by a grant from the International Health Division of the Rockefeller Foundation.

groups of elderly persons where the greatest amount of reinfection tuberculosis has been found to be present (15, 16). One of the purposes of the study described in this paper was to determine the incidence of new tuberculosis in such a group by means of periodic X-ray examination.

The second purpose of this study was to obtain additional information concerning the significance of findings and probable future course of the large number of cases found by surveys and other routine examinations which show lesions of the reinfection type, which either appear to be healed or whose activity cannot be immediately ascertained. Such cases are being found with increasing frequency, due to the large number of X-ray films which are now being made of apparently healthy people. In New York City, for example, over 400,000 survey X-ray examinations have been made during the past nine years. These have yielded many cases which fall into the above categories. The increasing use by many industrial concerns of routine chest X-ray films prior to employment and the roentgenography of all men prior to induction into the armed forces of the United States have also revealed many cases of this nature. It would seem of some importance to obtain further information concerning the probability of reactivation in cases such as these, in order to set up standards for their follow-up and to determine their suitability for normal employment.

METHODS

The group studied consisted of persons receiving public assistance in the form of Home Relief in the Kips Bay-Yorkville Health District. This area is situated in the middle East Side of Manhattan and contains a population of approximately 250,000, with an average of 8,000 adults on Home Relief at any one time. The annual tuberculosis death rate in this District in 1941 was 37 per 100,000. It may be stated that an intensive case-finding program has been under way in the District since 1927, and for this reason the prevalence of unknown tuberculosis in the area is probably less than in other sections of the City.

Our survey was made possible because of the full and enthusiastic coöperation of the Department of Welfare of the City of New York. First appointments to the clinic were issued by the case workers of the Welfare Department who had been previously informed of the purposes of the survey. Their clients were urged by them to visit the clinic on a purely voluntary basis, 60 per cent of those invited into the clinic by this method kept their first appointments, and an additional 12 per cent responded to a follow-up letter.

Only persons fifteen years of age and above were invited into the clinic for X-ray examination. All known cases of tuberculosis and known contacts, as well as persons who had received an X-ray film of the chest within the preceding six months, were excluded from this survey.

The original X-ray examination was on 14 × 17 inch paper film. Each film was read independently by two trained chest men.

Cases which showed tuberculous lesions of the reinfection type were divided into healed tuberculosis and clinically significant tuberculosis. All persons whose X-ray films showed well calcified lesions definitely due to reinfection tu-

berculosis, or areas of fibrosis which appeared well healed, were placed in the former group. The latter group included those whose X-ray film was of an obviously active appearance, showing cavitation or extensive soft infiltration, and also persons whose X-ray films showed fibrotic or infiltrative lesions, the activity of which could not be determined definitely from a single X-ray film.

All persons whose disease was classified as clinically significant were recalled to the clinic, where a careful history was elicited and a complete physical examination was performed. Certain of these cases were clearly active, as evidenced by the X-ray appearance, the finding of positive sputum or gastric washings, the presence of symptoms definitely those of tuberculosis or a change in the lesion subsequent to the original survey film. The disposition of these active cases presented no problem, as all were in need of institutional care and hospitalization was urged.

The cases whose activity was not definite at the time of the initial examination were carefully followed with frequent X-ray examinations (usually at monthly intervals) and repeated sputum examinations. Gastric washings were performed on all patients whose sputum was negative.

All persons classified as having healed pulmonary tuberculosis of the reinfection type were reëxamined at intervals ranging from three to twelve months. A minimum follow-up period of six months was regarded as necessary for the purposes of this study.

Persons whose original films were negative were requested to return for a second film at the end of a year; and wherever a sufficient length of time had elapsed, a third examination was made at the end of two years.

RESULTS

The survey was started in January, 1940. A total of 3,414 persons received their first X-ray examination during the next six months. The results of these examinations have been detailed in a previous paper (15). The following year all those whose films were originally negative were invited to return to the clinic for a second film; 1,726 persons responded to this invitation. At this time all adults who had been added to the Home Relief rolls in the District since the close of our first survey were also requested by their case workers to visit us for X-ray examination. After another year had elapsed, all members of both groups were invited to return once more for reëxamination. A total of 5,153 initial examinations were performed and a total of 3,244 annual reëxaminations were made of those with originally negative films.

The racial makeup of the group was as follows: white, 90.0 per cent; Negro, 6.81 per cent; Puerto Rican, 3.12 per cent. The amount of the various forms of reinfection tuberculosis did not differ sufficiently among the three groups to warrant statistical analysis of racial differences.

The findings at the time of initial examination have been combined for the two years, and are shown in table 1.

The age and sex distribution of those who have had annual reëxaminations is shown in table 2.

The 3,244 annual reëxaminations which were performed resulted in the discovery of a single new case of tuberculosis. It occurred in a girl twenty-one years of age.

Of the 136 cases which were diagnosed as significant tuberculosis, 34 were obviously active at the time of first examination or shortly thereafter. Of this

TABLE 1

Healed and significant reinfection tuberculosis found on first X-ray examination

AGE GROUP	MALE					FEMALE				
	Number in group	Healed tuberculosis		Significant tuberculosis		Number in group	Healed tuberculosis		Significant tuberculosis	
		Number	Per cent	Number	Per cent		Number	Per cent	Number	Per cent
15–19.9	237	0		0		267	0		0	
20–29.9	120	0		3	2.5	266	0		0	
30–39.9	306	10	3.3	8	2.9	495	7	1.2	7	1.2
40–49.9	391	9	2.3	25	6.4	541	12	2.2	6	1.7
50–59.9	527	34	6.5	27	5.1	621	30	4.8	11	1.8
60–69.9	478	48	10.0	28	5.9	605	44	7.3	9	1.5
70–79.9	152	21	13.8	5	3.3	121	7	5.8	4	3.3
80–85	15	5	33.3	0		11	3	27.3	0	
Totals....	2,226	126	5.7	96	4.3	2,927	103	3.5	40	1.4

TABLE 2

Sex and age distribution of persons having negative X-ray films on first examination; at the end of one year; and at the end of two years

AGE GROUP	X-RAYED FIRST YEAR			X-RAYED SECOND YEAR			X-RAYED THIRD YEAR		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
15–19.9	237	267	504	61	76	137	16	13	29
20–29.9	117	266	383	31	74	105	8	26	34
30–39.9	288	481	769	104	191	295	25	60	85
40–49.9	357	520	877	144	240	384	49	88	137
50–59.9	466	580	1,046	257	309	566	119	139	258
60–69.9	402	552	954	252	326	578	136	190	326
70–79.9	126	110	236	87	77	164	69	55	124
80+	10	8	18	6	9	15	3	4	7
Totals....	2,003	2,784	4,787	942	1,302	2,244	425	575	1,000

number, 12 had minimal tuberculosis, 16 had moderately advanced disease and in 7 patients the disease was far advanced.

Twenty-seven persons were admitted to institutions for the tuberculous and the remaining 7 received their treatment by the clinic personnel.

Ninety-three of the 102 cases classified as clinically significant, but not obviously active, were followed for a period ranging from six months to twenty-eight months, with an average follow-up of 15.6 months. Only one member of the

group gave a history of clinical tuberculosis in the past; this man of thirty-four had been discharged as arrested by a tuberculosis sanatorium four years previously. We obtained his previous films from the sanatorium and found that his disease had spread since his discharge His lesion has remained stationary, however, during the twenty-eight months he has been under our observation. For the past twenty-four months he has been working seven hours a day as a translator. He feels perfectly fit and we have now classified him as arrested. Two members of the group became active under observation, one a man aged thirty and the other a man aged sixty-seven. The lesion of the younger man showed a spread after five months' observation and that of the elder, eleven months after his first X-ray examination.

One hundred and ninety-five of the 229 cases diagnosed as having healed tuberculosis were followed for a period ranging from six months to twenty-eight months, with an average follow-up period of 18.8 months. One of these cases, a man of sixty-one, became active at the end of twelve months' observation.

The names of the 9 cases of significant tuberculosis and those of the 34 cases of healed tuberculosis whom we were unable to follow for a period exceeding six months were checked with the Central Tuberculosis Roster of the City of New York, in order to make certain that they had neither died of tuberculosis nor been diagnosed elsewhere in the City as having active disease during the period of the survey. However, no cases were found as a result of this investigation.

DISCUSSION

The amount of healed and significant tuberculosis found in this survey on original examination was approximately the same as that found in surveys of similar population groups, such as those conducted in New York City by Edwards and his associates (14).

The fact that only a single new case of tuberculosis was discovered in 3,244 annual reëxaminations would seem to indicate that this procedure is not economically justified in a group of the type studied. It will be noted, however, that only 685 reëxaminations, or 21.1 per cent of the total, were made of persons under forty years of age. Most workers agree that new tuberculosis occurs most frequently in younger persons and that the high prevalence of reinfection disease which has been found in those of advanced years is due to infections acquired earlier in life, when the opportunities for contact were more frequent. The absence of new tuberculosis in 2,559 annually reëxamined persons over forty with originally negative films would tend to substantiate this theory.

Perhaps the most noteworthy finding of this two-year survey and follow-up was the low rate of breakdown among persons whose X-ray films had showed lesions of the reinfection type, the activity of which was not manifest after a relatively short period of observation. Only one of 195 cases of healed tuberculosis became active during an average follow-up period of 18.8 months; and even in cases regarded as clinically significant, there were only 2 among 75 who exhibited definite evidence of activity during an average follow-up of 15.6 months.

The follow-up period on these cases has not been of sufficient length, nor has

the number studied by us been sufficiently large, to warrant the drawing of final conclusions. It is hoped that the opportunity which is being afforded investigators to study large numbers of cases of the types described in this paper will shed further light on the breakdown rates. Such cases are now being found in increasing numbers, particularly in the routine X-ray examinations of draftees, and are readily available for study. Until more data are available, it is felt that patients with X-ray lesions of the reinfection type which are not definitely active should not be prevented from engaging in normal employment so long as they remain under medical observation; for, as Brahdy (18) has recently pointed out, such discrimination "is steadily undermining the roentgenological case-finding campaign—the most effective antituberculosis weapon yet devised."

CONCLUSIONS

1. The results of an X-ray survey of 5,153 unemployed adults in New York City have been presented.

2. Of the males, 5.66 per cent and, of the females, 3.52 per cent showed healed tuberculosis, and 4.31 per cent of the males and 1.37 per cent of the females showed clinically significant tuberculosis at the time of first examination.

3. Annual reëxaminations of 3,244 persons with originally negative films resulted in the discovery of a single case of new tuberculosis.

4. One hundred and ninety-five cases of healed tuberculosis were followed for periods ranging from six to twenty-eight months, with an average follow-up period of 18.8 months. A single case was found to be reactivated after twelve months.

5. Of the 136 cases of significant tuberculosis, 36 were found to be active at the time of first examination or shortly thereafter; 93 of those which were not definitely active were followed for a period ranging from six to twenty-eight months, with an average follow-up period of 15.6 months. Two cases became active during this follow-up period, one after five months, the other after eleven months.

CONCLUSIONES

1. Preséntanse los resultados de un censo roentgenográfico de 5,153 desempleados adultos de la ciudad de Nueva York.

2. Al hacer el primer examen, 5.66 por ciento de los varones y 3.52 por ciento de las mujeres revelaron tuberculosis cicatrizada, y 4.31 por ciento de los primeros y 1.37 de las últimas, revelaron tuberculosis de importancia clínica.

3. El reexamen anual de 3,244 personas que revelaron al principio películas negativas, sólo puso de manifiesto un caso nuevo de tuberculosis.

4. Ciento noventa y cinco casos de tuberculosis cicatrizada fueron seguidos durante períodos de 6 a 28 meses, con un promedio de 18.8 meses, descubriéndose que sólo un caso revelaba reactivación a los doce meses.

5. De los 136 casos con tuberculosis de importancia clínica, 36 resultaron activos al realizarse el primer examen, o poco después; 93 de los no marcadamente activos fueron seguidos durante períodos de 6 a 28 meses, con un promedio de

15.6 meses. Dos casos se volvieron activos durante este período, uno a los cinco, y el otro a los once meses.

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CASE-FINDING

A Five-Year Study by the Denver Tuberculosis Society

VELMA V. SPAULDING[1]

In an effort to reduce tuberculosis by finding the disease in the early stages, the Denver Tuberculosis Society, with the approval of the Denver County Medical Society, began testing groups of apparently well people for tuberculosis in April, 1936. The present report is the result of testing from April, 1936 to September, 1941, approximately the first five years of the survey. Participation in the testing was voluntary. A total of 27,726 persons was tested. The number from each group is shown in table 1. The elementary school children were mainly from the Negro and Mexican districts, but the high school students came from all of the high schools of the city. Likewise, all of the colleges in the city took part. The tests were offered to teachers and other adults in the school on the same basis as to students. A few community groups were tested also. More than 80 per cent of the parents of the students included in the study were born in the United States.

Examinations for tuberculosis consisted of a Mantoux tuberculin test and an X-ray examination of the reactors. The tuberculin testing was done by three pediatricians skilled in this work. Human OT was used. It was obtained in concentrated form, 1 g. of OT in 1 cc. Mulford's brand was used exclusively. This was purchased on the open market and the expiration date was on the average of two to three years in the future. A dilution of 1:1,000 was made by the Research Department of the National Jewish Hospital and tested for potency by injecting 0.1 cc. intracutaneously into guinea pigs which were known to have tuberculosis. After such proof of potency, the 1:1,000 dilution was used for the Mantoux tests; 0.1 cc. containing 0.1 mg. of OT was injected intracutaneously on the lateral aspect of the flexor surface of the forearm. Results of the tuberculin tests were read approximately forty-eight hours after the testing. No charge was made for the tuberculin test.

By special arrangement, all X-ray films were taken at the National Jewish Hospital. One flat X-ray picture was available for each reactor. Those who could pay were asked to contribute $1.00 toward the expense of the X-ray examination. The X-ray films were read by a committee of three physicians, two of whom are clinical chest specialists and one an X-ray specialist.

The X-ray classification recommended by the 1940 subcommittee on Case-Finding Procedures in Tuberculosis of the American Public Health Association was used. In every instance where further examination or medical treatment was recommended by the physicians reading the X-ray film, the case was referred to the family physician or the Denver Tuberculosis Dispensary when a family physician was not available.

[1] Executive Secretary, Denver Tuberculosis Society, 314 Fourteenth Street, Denver, Colorado.

ANALYSIS OF THE DATA

Calculation of age: The age of each one participating under twenty years was calculated in years and months from date of birth to date of tuberculin testing. The meaning of age used in this study may be illustrated by the following: a student is regarded as fourteen years old and in his fifteenth year if his age falls within the boundaries of fourteen years and no months to fourteen years and eleven months inclusive.

Percentage of persons with tuberculin reactions: (Tables 1 and 2) Five thousand eight hundred and ninety-nine persons (21.2 per cent) of the total 27,726 tuber-

TABLE 1

Results of tuberculin tests by groups

GROUP	NUMBER TESTED AND READ	NUMBER POSITIVE	PER CENT POSITIVE
Public School			
Elementary	2,707	450	16.6
Junior high	10,662	1,763	16.5
Senior high	9,007	2,027	22.5
Total	22,376	4,240	18.9
Catholic School			
Elementary	990	165	16.6
High (9, 10, 11, 12 grades)	2,063	378	18.3
Total	3,053	543	17.7
Miscellaneous			
College students	444	138	31.1
Teachers and school nurses	437	308	70.5
Cooks, clerks and custodians at school	71	41	57.7
NYA			
Employees	1,119	503	44.9
Supervisors	43	25	58.1
Glenarm Y.M.C.A. (Negro)	75	50	66.6
Central Y.W.C.A.	108	51	4.72
Total	2,297	1,116	
Grand total	27,726	5,899	21.3

culin tested reacted to the tuberculin test; 2,933 (21.9 per cent) of the 13,377 males and 2,966 (20.7 per cent) of the 14,349 females were reactors. Apparently there was little difference between the sexes in respect to percentage of positive reactors for the total group. However, the males had a somewhat higher infection rate in every age group above that of ten years. This finding is in accord with that of Whitney and McCaffrey (1) reporting results of testing with PPD.

The prevalence of tuberculous infection in the high school population of Denver is among the lowest rates reported. It is about the same as for Chicago (2). Senior high school students of Denver showed 2,027 (22.5 per cent) and

junior high school students 1,763 (16.5 per cent) reactors. The children tested in the elementary schools were from the Mexican and Negro districts and their percentage of reactors (16.6 per cent) does not represent elementary school children as a whole in Denver.

Data for 4,960 students who reacted to the tuberculin test showed that 31 per cent had had contact with a tuberculous person.

TABLE 2

Results of tuberculin tests, by sex and age

April, 1936–September, 1941

SEX AND AGE ALL RACES	TOTAL TUBERCULIN TESTED	PER CENT POSITIVE	TOTAL X-RAY FILMS	FIRST INFECTION—X-RAY				REINFECTION—X-RAY					
				Negative	Suspect	Active	Inactive	Negative	Minimal	Moderately advanced	Far advanced	Arrested	Suspect
Both Sexes													
All ages	27,726	21.2	4,473	2,133	38	1,532	770	4,423	23	1	0	5	21
Under 5	43	4.7	3	1	0	1	1	3	0	0	0	0	0
5–9	1,748	12.8	208	123	4	77	4	205	1	0	0	0	2
10–14	12,510	15.9	1,591	787	2	745	57	1,575	7	0	0	0	9
15–19	11,978	24.1	2,111	1,015	20	585	491	2,096	9	0	0	1	5
20 and over	1,447	54.1	560	207	12	124	217	544	6	1	0	4	5
Male													
All ages	13,377	21.9	2,258	1,062	18	759	419	2,236	9	0	0	0	13
Under 5	23	4.3	2	1	0	0	1	2	0	0	0	0	0
5–9	875	12.0	101	67	2	28	4	100	0	0	0	0	1
10–14	6,025	16.4	790	383	2	371	34	783	2	0	0	0	5
15–19	5,806	25.4	1,110	502	6	317	285	1,101	6	0	0	0	3
20 and over	648	56.0	255	109	8	43	95	250	1	0	0	0	4
Female													
All ages	14,349	20.7	2,215	1,071	20	773	351	2,187	14	1	0	5	8
Under 5	20	5.0	1	0	0	1	0	1	0	0	0	0	0
5–9	873	13.6	107	56	2	49	0	105	1	0	0	0	1
10–14	6,485	15.6	801	404	0	374	23	792	5	0	0	0	4
15–19	6,172	22.8	1,001	513	14	268	206	995	3	0	0	1	2
20 and over	799	52.5	305	98	4	81	122	294	5	1	0	4	1

Data were available as to residence in Colorado for 4,390 students who had positive tuberculin reactions; 3,043 (69.3 per cent) of these students were born in Colorado. In addition, 648 (14.7 per cent) had lived in Colorado ten years or more. This information is of interest because Colorado is regarded as a "health resort."

The percentage of reactors (31.1 per cent) found in the three colleges in Denver compares favorably with that reported by Tice (2) for Chicago colleges. It is similar to results given by the Subcommittee on Case-Finding Procedures in

Tuberculosis of the American Public Health Association (3). The teachers, school nurses and other adults in the schools (cooks, clerks and custodians) presented higher percentages of reactors to the tuberculin test which can be explained largely on the basis of age.

The employees of the National Youth Administration were largely from the underprivileged groups and many were Spanish-Americans and Negroes. These facts probably account for the percentage which is higher than that of the college students of similar age.

Racial differences among students in percentage of infected persons: (Table 3) Racial origin was known for 8,582 boys and 9,322 girls of school age. The data were tabulated for the following groups: white, black, yellow, Mexican or Spanish-American and red Indian. It will be noted that the students of the black race showed much higher percentages of reactors than those of the white race; the students of Spanish-American or Mexican origin had more than twice

TABLE 3

Results of tuberculin tests, by race and sex (for students only)

RACE	MALE				FEMALE			
	Number positive	Per cent positive	Number negative	Total	Number positive	Per cent positive	Number negative	Total
White	1,719	21.2	6,401	8,120	1,700	19.4	7,069	8,769
Spanish-American or Mexican	94	48.4	100	194	95	40.2	141	236
Black	86	39.6	131	217	95	34.7	178	273
Yellow	12	24.0	38	50	8	18.5	35	43
Red Indian	1		0	1	0		1	1
Total	1,912		6,670	8,582	1,898		7,424	9,322

as large percentages as the white race. The small numbers of the yellow and red Indian races did not give sufficient bases for percentages.

Percentage of tuberculin reactors taking the X-ray examination: Of the tuberculin reactors 75.8 per cent had the X-ray examination under the plan outlined in this report. Some of the tuberculin reactors secured their X-ray films from private physicians. Others moved away and could not be reached for an X-ray examination.

Percentages of tuberculin reactors classified as first infection, active by X-ray appearance: (Table 2) Seven hundred and fifty-nine (33.6 per cent) of the males who had X-ray films under the plan described were classified as "active first infection X-ray;" 773 (34.9 per cent) of the females who had X-ray films were classified similarly.

Percentage of tuberculin reactors, classified as reinfection, positive by X-ray appearance: (Table 2) Twenty-eight females (1.3 per cent) of 2,215 X-rayed were diagnosed, as follows: minimal, moderately advanced, far advanced, arrested or suspect. Twenty-two males (1.0 per cent) of 2,258 X-rayed were

similarly diagnosed. Thus 50 individuals (0.2 per cent) of the total group tuberculin tested, or 1.1 per cent of all X-rayed were regarded as having reinfection. (It should be kept in mind that only 75.8 per cent of the reactors were X-rayed.)

Detailed study of X-ray findings in the chest: (Table 4) X-ray findings were classified in detail as to frequency for two of the five years covered by this report, that is for 1936–1937 and 1937–1938. The X-ray films taken during these two years were of students in both the junior and senior high schools and colleges and a small number of adults associated with them. The detailed classification shows the rarity of many other abnormal chest conditions.

TABLE 4

Detailed X-ray findings in the chest, by sex—for 1936–1937 and 1937–1938)

X-RAY FINDINGS	MALE	FEMALE
First infection (total X-ray films)	1,139	1,123
Negative	672	696
Positive	467	427
Suspect	0	0
Reinfection (total X-ray films)	1,139	1,123
Negative	1,129	1,116
Positive	3	4
Suspect	7	3
Ghon tubercles	133	135
Calcification of hilar and tracheobronchial lymph nodes	122	129
Nontuberculous abnormalities	48	53
Referral for primary tuberculosis infection	24	16
Referral for reinfection tuberculosis	10	7
Referral for heart	17	21

CONCLUSIONS

A total of 27,726 persons in Denver was tested for tuberculosis during a five-year period. While testing was done on a voluntary basis, the large number participating furnishes some interesting data as to trends and indications for examination. The high school group especially, representing all of the high schools in the city and composed of large numbers, gives a good indication of the tuberculosis situation among high school students in Denver.

The high school population shows one of the lowest percentages of tuberculin reactors reported; that is, 22.5 per cent reactors for senior high school students and 16.5 per cent for junior high school students. Since the majority of these children were born in Denver, it would seem that living in this "health resort" had not increased the liability to tuberculous infection beyond the liability existing in cities that are not health resorts.

Students representing the three colleges in Denver had 31.1 per cent reactors. This percentage compares favorably with other reports on college students.

The higher percentages of tuberculin reactions in the National Youth Ad-

ministration employees and adults in the study can be accounted for largely on the basis of lower socio-economic class, race and greater age.

The data on percentage of tuberculin reactions by age point to the importance of testing those of older age groups. The racial data present the need of concentrating the testing program on the Spanish-Americans or Mexicans and Negroes.

One thousand five hundred and thirty-two cases with active first infections, as revealed by X-ray examination, and 50 cases with reinfection tuberculosis may seem like a small number to be uncovered in tuberculin testing 27,726 persons and X-raying 75.8 per cent of the reactors. The study, however, was largely one of students. It should be pointed out that the program gave exceptional opportunities for tuberculosis education because everyone participating learned about the communicability of tuberculosis, the importance of diagnosing the disease early, the methods of finding early cases and the proper methods of treatment.

The study of frequency of X-ray findings for two of the five years included in the report shows the rarity of many nontuberculous abnormal conditions found in the chest.

SUMMARY

A total of 27,726 individuals in Denver, mainly students, were tested for tuberculosis during a five-year period.

Twenty-two and a half per cent of the senior and 16.5 per cent of the junior high school students showed tuberculin reactions.

College students presented 31.1 per cent positive reactors and NYA employees and other adult groups showed higher percentages.

In this group, 1,532 "active first infection" and 50 "reinfection" cases were uncovered by X-ray examination among the tuberculin reactors X-rayed (75.8 per cent of the reactors were X-rayed).

A study of frequency of X-ray findings presents the rarity of many abnormal conditions of the chest.

SUMARIO

Durante un quinquenio se comprobó, en cuanto a tuberculosis, a 27,726 individuos, principalmente estudiantes, en Denver.

Un 22.5 por ciento de los estudiantes avanzados de la escuela superior y un 16.5 por ciento de los principiantes, revelaron reacciones positivas a la tuberculina.

En los estudiantes universitarios los reactores positivos representaron 31.1 por ciento, mientras que los empleados de la Administración Nacional de Ayuda a la Juventud, y otros grupos adultos, revelaron porcentajes más altos.

En este grupo, los exámenes roentgenológicos pusieron de manifiesto 1,532 casos de primoinfección activa, y 50 de reinfección entre los reactores roentgenografiados (un 75.8 por ciento de los reactores lo fueron).

Un estudio de los hallazgos roentgenológicos demuestra la rareza de muchas anomalías torácicas.

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Case presented at the Diagnostic and Therapeutic Clinical Conference arranged by the American Trudeau Society, under the Chairmanship of Dr. Henry C. Sweany

LIPID PNEUMONIA[1]

ARTHUR M. STOKES[2]

J. H., age sixty-two, had had casual exposure to tuberculosis in 1920–1921. He had been a carpenter and/or stone mason from 1900 to 1941. The past history revealed symptoms of chronic sinusitis for several years; in June, 1939 he fell from a roof but an X-ray film at that time revealed no evidence of fractured ribs and no intrapulmonary lesion; in January, 1940 seven abscessed teeth were extracted and two more in January, 1941.

In November, 1940 he began to note undue fatigue, a loss of six pounds, one ounce of thin watery sputum and elevation of temperature to 99° or 100°F. By December the cough had increased, the sputum was blood-streaked on one occasion, he had night sweats and was physically unable to work.

On January 22, 1941, he visited the Out-Patient Department at which time the sputum was decreasing in amount but was becoming more purulent. There was slight tenderness in the right axillary region and some flattening of the middle third of the right chest where there was moderate dulness and suppression of breath sounds but there were no râles. An X-ray film made at that time showed a density in the apex of the right lower lobe. At bronchoscopy, two days later, secretions were noted coming from the bronchus of the right lower lobe. This examination was followed by increased cough and sputum, exertional dyspnoea and a low grade fever for two weeks. He was seen again February 12, 1941 when he had a further loss of weight, making a total of twenty-one pounds, and he had had occasionally streaked sputum. The physical signs were unchanged and he was admitted to the hospital following X-ray film shown in figure 1.

Four to six ounces of sputum were mucopurulent and contained spirochetes, fusiforms and gram-positive cocci. Aerobic cultures grew haemolytic *Streptococcus*, haemolytic *Staphylococcus aureus* and *Streptococcus viridans*. Anaerobic cultures grew a haemolytic and nonhaemolytic streptococcus. There were no pneumococci or tubercle bacilli. The red, white and differential counts were normal. A second bronchoscopy revealed no gross changes in the bronchi, but secretions were seen in the bronchi of the right lower and upper lobes. A biopsy from the dorsal branch bronchus of the right lower lobe showed only atrophy of the mucous membrane.

[1] Presented before the Medical Section at the 38th annual meeting of the National Tuberculosis Association, Philadelphia, Pennsylvania, May 8, 1942.

[2] Homer Folks Tuberculosis Hospital, Oneonta, New York.

Being unable to make a differential diagnosis between malignancy and abscess of the lung, an exploratory thoracotomy was done February 23, 1941. The apex of the right lower lobe was rounded and had the consistence of liver. A lobectomy seemed indicated and was carried out. The fissures were freed with difficulty and two firm nodules, measuring 1.5 cm., were noted on the lower surface of the middle lobe and the middle and lower lobes were removed. On cutting across the bronchi, there was no evidence of malignancy and the hilar nodes appeared normal.

The postoperative course was uneventful until March 11, 1941 which was the time of slough of the bronchial sutures. He had fever to 103°F. and developed a right apical empyema which was evacuated by tube drainage. Bronchoscopy

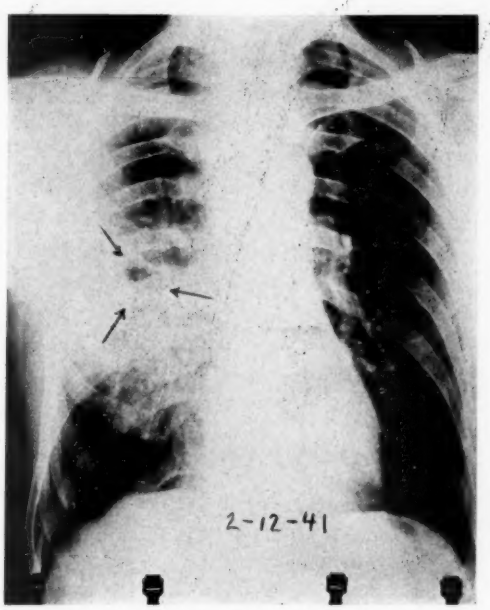

FIG. 1

on April 16, 1941 showed a fistula, 2 mm., in the bronchus of the right lower lobe; ten days later, a second appeared and on July 11, 1941 a pleural-bronchial communication was demonstrated by iodized oil. This, however, healed and the patient was apparently cured as of December 23, 1941 and has remained so.

The histological report of the lung, including the nodules in the middle lobe, showed thickened alveolar walls, alveoli filled with fibrin and polymorphonuclears, some areas undergoing necrosis, others organizing and still others carnified. There were occasional foreign body giant cells. Staining with sudan-III revealed the presence of a lipid substance in the alveoli (but it did not stain with osmic acid), and the final diagnosis was lipid pneumonia with abscess formation.

Having made the diagnosis the following additional history was obtained: for several years he had used vaseline freely in his nose upon retiring; for more than

a year he had used "Va-tra-nol." Also, it was interesting to learn at this time that he habitually slept on his right side.

SUMMARY

At exploratory thoracotomy, three surgeons so strongly suspected malignancy that the right lower and middle lobes were removed but histological study revealed a lipid pneumonia with abscess formation. A more detailed history may have suggested the aetiology and rendered the differential diagnosis less difficult.

THE NATURAL HISTORY OF TUBERCULOUS TRACHEOBRONCHITIS[1]

DAVID SALKIN, A. V. CADDEN AND R. C. EDSON

Tuberculosis of the trachea and bronchi has been described pathologically for over one hundred years but clinically for only a few years. The recent interest has been due to the more liberal use of the bronchoscope in a disease which has been regarded as a foremost contraindication to endoscopic examination. Just as in any other field of medical investigation still in its infancy no one view is held uniformly and the literature is full of divergent opinions on the incidence of the disease in the living and in the dead, its pathogenesis, progress, ability to heal, symptoms, prognosis and treatment.

There is a definite need for a control series. It must not be too small; it must comprise a group of cases admitted during a definite period of time; it must be observed frequently; and it must be followed for a sufficient length of time. In a chronic disease, such as tuberculosis, a control series should be observed for at least ten years. However, in this study a clue to the phases mentioned above is obtained, since the oldest cases have been observed for a period of five years and the youngest cases for fifteen months.

The study is composed of two parts: a group of 125 consecutive autopsies and another group of 622 consecutive admissions observed during the same period of time. In the autopsy group emphasis is placed on the incidence, pathology and symptoms observed. In the clinical group the chief points emphasized are incidence, classification, symptoms, course, prognosis, mode of healing and the results of stenosis.

AUTOPSY STUDY

The postmortem study is based on 125 consecutive autopsies performed on cases dying from pulmonary tuberculosis at Hopemont Sanitarium over a period of four and one-half years, from June, 1937 to January, 1941, corresponding in time with the clinical study. Most of these cases were not bronchoscoped during life and did not form part of the clinical control group. Gross dissection of the laryngo-tracheobronchial tree was extended frequently to the tenth or twelfth subdivision and into bronchi measuring one or two millimeters. The study is expecially one of gross observation with microscopical confirmation. All tuberculous lesions were noted with the exception of those at the caverno-bronchial junction which showed specific alterations in all cases. Since the pathology of tuberculous bronchitis is well known, only those phases will be mentioned which have a special bearing on this study.

In the 125 cases examined, tuberculous lesions in the trachea, large and medium sized bronchi were present in 50, or 40 per cent. This figure was not fixed but found to be influenced by three factors, namely, the predominant char-

[1] From the Hopemont Sanitarium, Hopemont, West Virginia, and the University of West Virginia Medical School, Morgantown, West Virginia.

acter of the disease, its lobar location and the sex of the patient. The details are presented in table 2. The exudative cases present the highest incidence of tracheobronchitis, then the mixed cases and then the fibroid. The high incidence of bronchitis in lower lobe disease is noteworthy. The age of the patient and the duration of the disease were of no significance.

The lesions commonly seen included all varieties of ulcers, submucosal nodules, fibrous and inflammatory stenoses. Both ulcerative and non-ulcerative types occurred together and the frequency of stenoses depended chiefly upon the extent of the dissection of the smaller bronchi. The ulcers showed a general distribution in 64 per cent of the cases, located chiefly on the posterior wall in 24 per cent and on the anterior wall in 12 per cent. The size of the diseased bronchi was such that they could be seen with a bronchoscope in 84 per cent of the cases and in 16 per cent they were beyond endoscopic view. Table 1 shows the incidence of some of the complications in the groups with and without tracheobronchitis. It may be seen that the cases with tracheobronchitis showed a higher incidence of tuberculous lesions in the larynx, intestines, spleen and liver and

TABLE 1

Percentage incidence of complications in the autopsy group

	(50) CASES WITH TRACHEOBRONCHITIS	(75) CASES WITHOUT TRACHEOBRONCHITIS	RATIO
Bronchiectasis	20	36	0.5 to 1
Blocked cavities	10	9	1.1 to 1
Atelectasis	28	21	1.3 to 1
Intestinal tuberculosis	70	50	1.4 to 1
Splenic tuberculosis	30	19	1.5 to 1
Hepatic tuberculosis	17	11	1.5 to 1
Caseation in lymph nodes	35	20	1.7 to 1
Laryngeal tuberculosis	67	23	2.9 to 1

a greater degree of caseation in the tracheobronchial lymph nodes. Atelectasis was also more common in the positive group. In 11 cases of the negative group no bronchiectasis or bronchial obstruction was present to account for the atelectasis, only small amounts of sputum and nonspecific bronchial catarrh were noted. Bronchiectasis strangely occurred more frequently in the negative group. The 51 cases with tuberculous laryngitis showed an associated 60 per cent tracheobronchitis and the 74 normal larynges 24 per cent.

No symptom, or group of symptoms, was found to be pathognomonic of tracheobronchitis, although the bronchitis group did show a higher incidence (table 3). The "suggestive" symptoms mentioned include unusually severe cough, variable and copious sputum and substernal discomfort. The reason for the presence of all these symptoms in the negative group may be ascribed to (*1*) extensive parenchymal disease, (*2*) secretions in the bronchial tree, (*3*) nonspecific oedema due to irritation by sputum and cough, (*4*) the presence of bronchiectasis in 36 per cent of the cases, and (*5*) the frequent occurrence of generalized and localized emphysema.

It appears that tuberculous bronchitis, like any other complication, is a manifestation of a more malignant type of infection and represents a severer type of

TABLE 2

Incidence of tracheobronchitis in autopsy and clinical groups

		CLINICAL GROUP		AUTOPSY GROUP	
		Number of cases	Per cent positive	Number of cases	Per cent positive
Total incidence		622	15.5	125	40
Predominant character of of the lesion	Exudative	244	22.5	98	42
	Mixed	356	10.4	23	26
	Fibroid	22	22.7	4	25
Lobar location	Upper lobe	573	13.4	116	38
	Lower lobe	49	40.8	9	66
Sex	Male	236	14.9	58	31
	Female	386	16.0	67	48
Extent of the disease	Minimal	33	6.0		
	Moderate	127	7.0		
	Far advanced	462	18.6		
General symptomatology of the patient	A. Mild	38	2.6		
	B. Moderate	536	15.4		
	C. Severe	48	27.0		
Positive sputum and cavity	Present	484	18.1		
	Absent	138	6.5		

TABLE 3

Percentage incidence of symptoms in cases with normal bronchi and tuberculous bronchi

TOTAL NUMBER OF CASES	CLINICAL STUDY		AUTOPSY STUDY	
	Normal bronchi (525)	Tuberculous bronchi (97)	Normal bronchi (75)	Tuberculous bronchi (50)
Wheezing	9	39	25	37
Rhonchi	13	33	25	37
"Suggestive" symptoms	12	33	40	50
Tuberculous laryngitis	6	17	23	67
Atelectasis	12	36	19	30
Bronchiectasis	8	14	36	20
Blocked cavities	6	9	9	10
Unexplained positive sputum	1	15		
Unexplained haemoptysis	2	9		
Unexplained spreads	3	8		

tuberculosis; in this small group about half again as severe as the cases without bronchitis.

CLINICAL STUDY

Every new case admitted to Hopemont from June, 1937 till March, 1941 was bronchoscoped within a few days after admission and before any treatment of the pulmonary disease was begun. Observation of all cases was extended to June, 1942. Thus, the oldest cases have been under observation for five years and the newest ones over one year. At the medical staff conferences the bronchoscopy results were not disclosed, so as not to influence the treatment of the cases.

This group comprises 622 cases. After the initial routine bronchoscopy the negative cases were reëxamined only when suspicious symptoms or signs appeared, prior to operative procedures such as pneumonolysis or thoracoplasty, failure of a lung to reëxpand after pneumothorax therapy, the occurrence of an unexplained spread or a positive sputum, or the suspected presence of a coexisting bronchiectasis. The positive cases were bronchoscoped every three to six months. The entire group was bronchoscoped over 2,000 times giving an average of three examinations per case. (This included 77 cases which died and 185 cases which now have active disease.) Some cases were examined over ten times.

The average period of observation for the entire group (including deaths) was thirty-two months. The 1937 group was observed for an average of forty-five months, the 1938 group for thirty-five months, the 1939 group for thirty months and the 1940 group for twenty-four months. During this period there were actually 697 admissions but only 622 cases were examined. The 75 cases not included in this series were moribund and died shortly after admission. However, many very ill patients were examined routinely, as is evident from the fact that thirty-two per cent of the cases were "far-moderate" and twenty-two per cent "far-far" in extent.

Diagnosis: The diagnosis of tuberculous lesions in the tracheobronchial tree is often hazardous and, no doubt, the difference between a specific and an nonspecific lesion may be very fine indeed. For our criteria we used the classical descriptions established by various authors, repeated examinations, cases followed to the autospy table and studies made with Dr. Waitman F. Zinn. Biopsies were performed only several times, for it was felt that the open area could become a focus of spread. Special care was used in excluding such nontuberculous lesions as are associated with extensive bronchiectasis, irritative sputum, unusually severe cough and allergic phenomena. Some cases were difficult to allocate properly and were reëxamined until they were suitably classified. It was assumed that all fibrotic stenoses were of tuberculous origin unless associated with extensive nontuberculous bronchiectasis.

One can be fairly safe in assuming that almost all of the minute bronchi about a caseous or cavernous focus show tuberculous involvement microscopically. In the major bronchi visualized by the bronchoscope the incidence given by various authors ranges from 3 per cent to 30 per cent (1, 2, 3). The small bronchi "around the corner" have undoubtedly a higher involvement.

It is well known that pathological and physiological disturbances resulting from disease in the major bronchi may be very great. It is not well known how important are the changes which occur as a result of disease in the small and microscopical bronchi. We suspect that they are very great and that, from the therapeutic standpoint alone, they may not only increase the severity of the disease but also affect closure of some cavities and so help the control of the disease.

We wish to stress that this study, like all others of a clinical nature, is not one of bronchitis generally, but only of tracheitis and bronchitis of the major bronchi. We regard tuberculous bronchitis as composed of three divisions, namely: (*1*) the endoscopic tree which can be well studied bronchoscopically and includes only the major and some medium sized bronchi, (*2*) medium and small bronchi which have been observed only indirectly by bronchography, (*3*) minute and microscopical bronchi which do not lend themselves to clinical observation and therefore our knowledge of them is inferential and vague.

Incidence of tracheobronchitis: The number of cases examined was 622, of which 64 (or 10 per cent) showed a tuberculous lesion on the first examination. Eventually 33 more cases showed positive bronchial findings. Thus, 97 cases, or 15.5 per cent of the group, showed a tracheobronchitis. This figure represents the incidence as found in a five-year study. It is not an absolute figure, for it depends upon certain factors such as the predominant character of the disease, its lobar location, extent, general symptomatic severity, the presence of positive sputum and cavity and the length of the period of observation. Factors of no importance are the sex of the patient, the duration of the symptoms and the year-period of observation.

Table 2 presents in detail the factors influencing the incidence of tracheobronchitis. Exudative disease showed twice as much bronchitis as mixed disease; the fibroid cases were too few in number to evaluate properly. The extent of the disease is of great importance, as the far advanced cases show three times as much bronchitis as those with minimal and moderately advanced lesions. The general incidence of 15.5 per cent holds only for this series composed of 75 per cent far advanced cases. The general symptoms shown by the patient are also of great significance and the more severe the symptoms the greater was the incidence of bronchitis. Out of a total group of 123 cases with severe symptoms, only 48 could be examined; the other 75 were terminal. If these 75 cases could also have been examined, the clinical incidence of bronchitis would have been still higher.

The cases with a positive sputum and cavity showed an incidence three times as high as those with a negative sputum and no cavity. Lower lobe tuberculosis showed three times as much bronchitis as that of the upper lobe. The important causes for this phenomenon may be (*1*) the greater endoscopic visibility of the lower lobe bronchus and (*2*) the stagnation of positive sputum in the lower lobe bronchi. The high incidence of bronchitis in the lower lobe cases in the autopsy group emphasizes the latter factor. Sex proved to be of no importance in influencing the incidence in the clinical group, although it was of some impor-

tance in the autopsy group; this may be due to the small number of cases in the latter. The duration of symptoms prior to admission was of no importance.

The percentages of positive cases found in the various years admitted, such as 1937 to 1941, were similar. The average age for both positive and negative cases was twenty-eight years. The age groups up to forty years showed no significant differences; the 17 cases over forty showed a higher incidence but were too few in number for proper comparison.

Another important factor in the incidence is the length of the period of observation. The longer this clinical group was observed the greater was the number of cases with bronchitis found. At first only 10 per cent of the cases showed bronchial disease but during the next five years an additional 5 per cent became positive, giving an annual increase of 1 per cent during this period. These new cases were found among those having progressive pulmonary disease, active uncontrolled lesions and among a group in which the bronchitis was first noted after control of the parenchymal lesion.

As in the autopsy study, the incidence of bronchitis clinically is not a fixed figure but is a fluid number depending upon several important factors and varying from 2.6 per cent in the cases with mild systemic symptoms to 40 per cent in lower lobe disease.

Relationship of bronchitis to laryngitis: Not only can one expect a greater incidence of tracheobronchitis in cases with tuberculous laryngitis but the reverse also holds true and cases with bronchitis show a higher incidence of laryngitis. In the 525 negative cases, laryngitis occurred 35 times (6.6 per cent) including 6 ulcerative and 29 non-ulcerative lesions. In the 97 positive cases, there were 17 cases of laryngitis (17.5 per cent) including 5 ulcerative and 12 non-ulcerative lesions. There was a total of 52 cases of laryngitis (8.3 per cent) in the entire series.

Classification: At the present time there are so many classifications that it is difficult to compare two groups of cases presented by different authors. There is certainly a need for a simple but adequate classification. Anatomical studies show that the disease is rarely localized but usually begins in the small bronchi and spreads to the larger ones. Ulceration and submucosal nodules occur in every variety and side by side. The bronchoscopist observes only part of the entire picture; he may see only submucosal nodules, but just out of sight extensive ulceration may be present.

The important observation to be made endoscopically is the presence or absence of a tuberculous lesion. Since known ulceration has great clinical importance in the production of a positive sputum we have divided the cases as ulcerative and non-ulcerative. One must remember, however, that (*1*) the major bronchi may show no ulceration and the minor ones be heavily ulcerated and (*2*) an area may be submucosal, then ulcerated, then again covered with mucosa a few weeks later. Some linear and superficial ulcers associated with a tuberculous nodule may themselves be nonspecific, due to added infection and the trauma of severe cough, and may show rapid healing.

The stenoses observed were of two types: (*1*) a true fibrotic stenosis which

represents an end-result of a localized inflammatory process and which may coexist with adjacent ulceration or active submucosal disease; and (*2*) a stenosis due to inflammatory swelling, which is relative and depends upon the size of the bronchus and the degree of the localized reaction, and is capable of being converted later to either a true stenosis or to an almost normal appearance. All intermediate degrees between the two types may exist. Stenosis is only a part of the disease process but deserves a special place clinically because of the important complications which may result from it.

The classification we use follows:

1. *Non-ulcerative:* includes local submucosal infiltration, diffuse submucosal infiltration, tuberculoma without ulceration.
2. *Ulcerative:* includes local or discrete ulcers, diffuse ulceration, hyperplastic ulcerous tumors.
3. *Stenosis:* (*a*) inflammatory (*b*) fibroid. These may be associated with any variety or combination of the ulcerative and non-ulcerative lesions.

The classification of the 97 positive cases is as follows:

	Cases	*Per cent*
Ulcerative—40 cases:		
Diffuse	35	36
Discrete	5	5
Non-ulcerative—57 cases:		
Diffuse	46	48
Discrete	11	11
	97	100
Associated stenoses:		
Inflammatory	33	34
Fibroid	10	10

In the non-ulcerative group there were 6 cases which had a controlled parenchymal lesion but a positive sputum, and though bronchoscopy showed a non-ulcerative lesion we suspected ulceration "around the corner."

Symtoms and signs: There are no pathognomonic symptoms and signs of tuberculous bronchitis but certain ones do occur with greater frequency with an involved tree as compared with the normal one. They are enumerated:

(*1*) Cough: unusually severe, paroxysmal and worse in damp weather.
(*2*) Expectoration: may vary considerably in amount from one period to another and appear to depend upon (*a*) the degree of both tuberculous and nontuberculous inflammation, (*b*) changes in degree of stenosis, if present, and (*c*) the weather which aggravates symptoms in cold, damp weather and improves them in warm, dry weather.
(*3*) Sputum: may be very thick and tenacious, ropy and occur as plugs.
(*4*) Discomfort: may be substernal or parasternal and usually localized to a

small area. It may be described as a pulling sensation, an itching, or a burning, but rarely as actual pain.
(*5*) Wheezing: may be very loud and may be heard best with the naked ear on expiration; may be substernal or localized vaguely to the upper or lower anterior chest wall; may be described as a rattling, bubbling or a sense of fulness.
(*6*) Dyspnoea: usually out of proportion to the amount of lung tissue involved, often paroxysmal and described as "asthmatic."
(*7*) Cyanosis: same features as mentioned with dyspnoea.
(*8*) Rhonchi: if localized, persistent and coarse suggest a bronchial obstruction of some nature.
(*9*) Unexplained positive sputum: this is one of the most important clues to a bronchitis when it is felt definitely that the pulmonary disease is not active.
(*10*) Unexplained haemoptysis: where it is felt that the parenchyma is not active. Bronchograms are then essential to rule out a bronchiectasis.
(*11*) Unexplained spreads: occurring after apparent control of the parenchymal disease or during apparently successful treatment.

When one or more of these symptoms are unusually pronounced the case was regarded as showing suggestive symptoms of bronchitis. All the symptoms occurred in both groups but with greater frequency in the one with bronchitis. Table 3 shows the incidence of these symptoms in the cases with and without bronchitis.

Roentgenological signs: These were mainly four in number:

(*1*) Blocked cavities as described by Salkin, Cadden and McIndoe (4). They occurred in 6 per cent of the group with normal bronchi and in 9 per cent of that with diseased bronchi.
(*2*) Evidence of bronchial irregularities shown by overexposed films, Bucky films, tomograms and bronchograms.
(*3*) Atelectasis or a uniform airlessness of a lung, a lobe, or part of a lobe. Small patchy lobular areas were not included because of the difficulty in differentiating them from true spreads, although we have seen some striking examples and believe that it occurs quite frequently. It was present in 12 per cent of the negative group and 36 per cent of the positive cases. It occurred in both groups both as a constant and intermittent feature and after pneumothorax, phrenicotomy and thoracoplasty. In comparing the incidence of atelectasis in the autopsy and clinical groups (table 3), it is seen to be higher in the latter. This may be due to the fact that by the time the patient had died the previously atelectatic area may have been included in a progressive caseous and cavernous process.
(*4*) Bronchiectasis, as proved by bronchograms and showing saccules and dilatations large enough to be of clinical significance. Since relatively few bronchograms were made, the figures are not indicative of its frequency but the same indications for bronchography (chiefly upper lobe) were used in both groups. In the negative group significant ectasia was present in 43 cases (or 8 per cent)

and in the positive group in 14 cases (or 14 per cent). Most of the saccules and dilatations were present at the site of the parenchymal disease but in about 21 per cent of both groups they occurred chiefly distal to the main pulmonary lesion.

Differential diagnosis of certain symptoms: Certain symptoms are such common accompaniments of tracheobronchitis that it is of value to review their frequency as found in this study:

(*1*) Wheezing occurred persistently in 88 cases, of which 44 per cent were associated with a tuberculous bronchitis and 56 per cent with bronchial secretions, nonspecific bronchitis, bronchiectasis and emphysema.
(*2*) Rhonchi occurred in 104 cases as follows: nonspecific bronchitis in 48 per cent, tuberculous bronchitis 31 per cent, bronchiectasis 13 per cent, emphysema 1 per cent, unknown 7 per cent. One of our most striking cases with unusually loud rhonchi showed normal bronchi at autopsy and only the presence of sputum probably accounted for this sign.
(*3*) Atelectasis occurred in 101 cases as follows: nonspecific bronchitis in 46 per cent, tuberculous bronchitis 36 per cent, bronchiectasis 4 per cent, unknown 14 per cent. Four cases presenting a lobar atelectasis and no tracheobronchitis during life came to autopsy; in 3 cases no bronchial lesions of any kind could be seen and in one case only the trachea showed ulceration but the bronchi were normal.
(*4*) The syndrome of wheezing, rhonchi and atelectasis together occurred in 31 cases as follows: tuberculous bronchitis 48 per cent, nonspecific bronchitis 43 per cent, bronchiectasis 6 per cent, suspected tuberculous bronchitis 3 per cent. If to this syndrome is added an unexplained positive sputum in the presence of an apparently controlled parenchymal lesion the probability of a tuberculous tracheobronchitis is much greater.

Course and progress of tracheobronchitis: This will be discussed under five headings dealing with the relationship of the bronchial disease to the parenchymal disease: (*1*) deaths, (*2*) active parenchymal disease, (*3*) improved parenchymal disease, (*4*) inactive parenchymal disease and (*5*) an inactive parenchyma but an active bronchus. The groups were observed respectively for seventeen, twenty-nine, thirty, forty-two and forty-four months and averaged 4, 4, 5, 6 and 10 bronchoscopies.

(*1*) Deaths: There were 17 deaths in this group. All cases showed progressive disease clinically and the 8 cases which came to autopsy confirmed the progressive nature of the bronchitis.

(*2*) Active parenchymal disease: There were 32 cases in this group but only 24 were observed sufficiently. In these cases the parenchymal disease remained stationary, progressed or improved partially. Under such circumstance, 6

cases showed progressive bronchitis, 18 cases remained essentially active though some showed repeated relapses and remissions. Not one case showed a permanent improvement in this group. When the pulmonary lesion was active, the bronchitis was also active. These cases had several periods of remissions—shallow ulcers appeared and then disappeared in three or four weeks, localized areas of submucosal nodules appeared and then almost disappeared in several weeks; swellings and injections became worse and then improved in short periods of time, and inflammatory stenoses appeared and also improved. Treatment by any method during such remission may cause erroneous conclusions. Evaluation must be made only after prolonged observation for a minimum of one year.

(*3*) Improved parenchymal disease: The term improved, as used here, means parenchymal disease which shows no cavity, a lesion which is regressing favorably and is consistent with healing and a negative sputum. If the sputum is positive, then it is presumably due to the bronchitis. This group included 11 cases, of which 9 were observed for a sufficient length of time. With the parenchyma improved, one case showed a progressive bronchitis, one case showed essentially no change and the other 7 cases showed a steadily improving bronchial lesion.

(*4*) Inactive parenchymal disease: The term inactive, as used here, means an inactive, arrested, roentgenologically stable lesion without pulmonary cavity. Any positive sputum presumably comes from the bronchial lesion. This group comprised 16 cases and 15 of them were followed for a sufficient period of time. In this group, as the parenchymal disease became inactive, 2 cases of bronchitis progressed, one case showed no change and 12 cases showed improvement. Thus, with an inactive parenchyma, 80 per cent of the cases with bronchitis improved and remained inactive during the period of this study.

(*5*) Inactive parenchymal disease with developing active bronchitis: This unusual group of cases showed no symptomatic or bronchoscopic evidence of bronchitis on admission. Then, some time after the parenchymal lesion became inactive, suspicious symptoms appeared and bronchoscopy revealed an active bronchitis. The usual symptoms were cough, expectoration, a positive sputum, streaking, wheezing and rhonchi, a new parenchymal lesion or atelectasis of a lobe. The appearance of any one or several of these was used as an indication for bronchoscopy. It is probable that these cases had an active lesion in the small bronchi beyond endoscopic vision and the activity progressed despite an improved or healed parenchymal focus and became evident some months later. This group comprised 21 cases, of which 18 were observed sufficiently; the other 3 cases were observed for less than six months and were not included. The time for the symptoms to appear after the parenchymal lesion became inactive varied from three months to four years, with an average interval of eighteen months. These cases showed very strikingly the first appearance of the bronchitis in the

"endoscopic tree," the progress of the lesion and its gradual (though usually stormy) regression and healing. In this group, one case remained stationary, 3 cases showed continued progression of the bronchitis and 14 cases showed an eventual spontaneous improvement and healing.

Thus, 77 per cent of these cases improved spontaneously! Some of them showed severe progress for a time and spread up the tree into the trachea, but eventually the inflammation subsided. Pulmonary spreads and presumably lobular atelectasis occurred frequently. These cases were treated mainly by further bed-rest or, at the most, by modified bed-rest. Perhaps, with further observation, some of these cases may again become active. Our experience with several other such cases, not a part of the control study, suggests that the eventual prognosis depends upon any new pulmonary spreads; such new lesions often heal, may progress and cause death, or become chronic with recurring remissions and relapses.

We feel that this group of cases should have an absolute minimum of one year's observation for proper evaluation. Several of these cases showed progression

TABLE 4

The fate of the bronchitis compared with the fate of the parenchymal lesions (83 cases)

PARENCHYMAL LESIONS	TOTAL	BRONCHITIS				
		Worse	Same	Improved	Per cent improved	
Patients died	17	17	0	0	0	
Active	24	6	18	0	0	
Improved	9	1	1	7	78	79
Inactive	15	2	1	12	80	79
Inactive but active bronchus	18	3	1	14	78	
	83	29	21	33		

of the disease for two years before improving, although some showed improvement after only six months. Of course, local treatment in such cases may give rise to erroneous conclusions.

Table 4 presents in detail the results discussed. In the whole group, regardless of the fate of the parenchymal lesion, the bronchitis became worse in 34 per cent, did not change in 25 per cent and improved in 41 per cent. Of course, these figures do not tell the entire story as they may change considerably depending upon the result obtained with the parenchymal lesion. No permanent improvement occurred in the cases which died and in those where the parenchymal lesion remained active. Where the parenchymal disease improved or became inactive the bronchitis improved in 79 per cent. In the entire group with improved and inactive parenchymal disease (including the fifth group mentioned) the bronchitis improved ultimately in 78 per cent of the cases.

It must be stressed that local treatment of a group of cases with bronchitis,

in the face of a controlled parenchymal lesion, should give at least 80 per cent good results before it can be regarded favorably. The acid test of a local treatment would lie in the active parenchymal cases, provided that the bronchi remained improved while the parenchymal disease remained active. Temporary improvement following even a simple bronchoscopy and aspiration is seen frequently in many cases regardless of the parenchymal status.

Prognosis: In determining the fate of the cases in this study we have used the terms active, improved and inactive to include the status of both the parenchymal and the tracheobronchial lesions. Since tracheobronchitis is so intimately connected with the course of the parenchymal lesion and since the bronchitis itself can form new foci of parenchymal disease, it was felt that this grouping was necessary. Thus, the terms improved and inactive were used to include both a healing or healed parenchyma and a healing or a healed bronchitis, if

TABLE 5

Final status of the bronchitis and negative cases

STATUS OF PATIENT	NORMAL BRONCHI (525)		BRONCHITIS (97)	
	Number of cases	Per cent	Number of cases	Per cent
Dead	60	11.4	17	17.5
Active	151	28.8	34	35.0
Improved	59	11.2	30	31.0
Inactive	255	48.6	16	16.5
	525	100.0	97	100.0

Total improved and inactive:

Negative group	59.8%
Bronchitis group	47.5%
Ratio	1.25 to 1

present. The term active was used to include both an active parenchymal lesion and an inactive lesion if an associated bronchitis was active.

It was noted that the cases with bronchitis usually had a more severe course but eventually the results were about 80 per cent as good as those without bronchial disease (table 5); or, the prognosis of the group with normal bronchi is 25 per cent better than that of the bronchitis group. Bronchitis acts in a twofold manner in that (*1*) it tends to produce spreads by virtue of the presence of an active tuberculous focus, especially if associated with a positive sputum; on the other hand (*2*) we have seen cavities in such cases close with great rapidity in significant numbers. Bronchitis may thus have both a favorable and an unfavorable effect upon the parenchyma.

A study of the negative and positive bronchial groups shows them to be fairly comparable with regard to such factors as extent of parenchymal disease, character of the lesion, symptomatic severity, presence of cavity and positive sputum, and collapse measures used.

Minimal, moderately advanced and far advanced disease occurred in 6 per cent, 22 per cent and 72 per cent in the negative group, and in 3 per cent, 8 per cent and 81 per cent respectively in the positive group. Exudative disease occurred in 37 per cent of the negative group and in 57 per cent of the positive group; mixed disease occurred in 60 per cent and 37 per cent respectively; and fibroid disease in 3 per cent and 6 per cent. In the negative group 7 per cent had no symptoms, 86 per cent had moderate symptoms and 7 per cent had severe symptoms, whereas in the positive group the figures were 1 per cent, 85 per cent and 14 per cent. Positive sputum and cavity occurred in 76 per cent of the negative group and in 90 per cent of the positive group. Collapse measures were used in 68 per cent of the negative group and 74 per cent of the positive group. The various types of collapse measures were similar in both groups with the exception of pneumothorax which was done in 69 per cent of the negative group and in 84 per cent of the positive group.

Mode of healing of tracheobronchitis: A healing non-ulcerative submucosal lesion shows a gradual decrease in the injection and swelling, the nodules become less marked, the mucosa becomes less irritable, less friable and the wall becomes more elastic. For some time the mucosa appears thickened and puckered, somewhat friable and inelastic. Such a picture may persist for months and years in extensive lesions. Milder lesions may revert to an almost normal appearance. In very extensive lesions the generalized oedema may first disappear leaving single nodules which then decrease in size with resultant irregularities and perhaps stenoses. Although such healing may occur rapidly, it is rare in less than six months and usually takes from six months to two years or more. One may expect some residual bronchoscopic signs of the inflammatory process in the great majority of cases for a long period of time.

A healing ulcerative lesion usually becomes non-ulcerative. If the defect is great then considerable scarring occurs. The chronic single ulcer shows a gradual shelving of its edges with central fibrosis. Shallow, confluent ulcers usually show first a reduction of the oedema and injection, then the ulcers become covered with mucosa and converted to a non-ulcerative lesion. Large hypertrophic masses usually heal with considerable scar formation and stenosis.

In this group of 34 cases of improved bronchitis, 17 cases were originally ulcerative and 17 non-ulcerative. Residual and significant stenoses occurred in 10 cases.

Bronchostenosis: The presence of any inflammatory lesion of appreciable depth in the tracheobronchial tree produces some degree of narrowing. A small degree is of little or no significance and barely perceptible in the trachea and large bronchi but is of great importance in the smaller bronchi. A partial bronchostenosis is, therefore, a relative phenomenon depending upon the degree of narrowing and the size of the bronchus. In this group we have considered an area as stenosed when there was an appreciable reduction in the size of the lumen, usually about one-third to one-half of the normal tree at that particular level. The stenoses in the finer bronchi, as seen by bronchograms, were numerous but

in this group only those were considered which came within bronchoscopic range. This is, therefore, a study of stenoses in the relatively large bronchi.

As a bronchial lesion heals there may be a decrease in the degree of stenosis caused by the subsiding inflammation and the final end-result depends upon the amount of fibrosis in the bronchial wall, which probably is progressive in most cases. The stenosis is most often circular when viewed "head on" but may be irregular; longitudinal section usually shows an irregular lumen.

The chief effects of a bronchostenosis are: (*1*) production of bronchiectasis, (*2*) production of an obliterative bronchitis starting in the smaller bronchi and extending to the larger ones, (*3*) production of an obstruction syndrome with retention of sputum which may produce acute symptoms resembling abscess, and (*4*) production of tension and blocked cavities.

Bronchograms in fibrotic stenosis: Bronchograms were made in 10 cases with fibrotic stenosis. In this group 2 cases showed a normal bronchial tree distally, 3 showed an obliterative process and 5 showed a distal bronchiectasis.

By *obliterative* bronchitis we mean a marked decrease in the size of the lumina of the distal bronchi, tortuosity and a complete failure of the still finer branches to fill. In these 3 cases bronchograms were made annually and eventually showed an increase in the lumen of the medium sized bronchi with production of irregular cylindrical and saccular dilatations—a typical bronchiectasis! This shows a striking picture of the gradual conversion of a bronchitis to a bronchiectasis. It is not surprising for, as a result of the destruction of portions of the bronchial wall, dilatation may be expected. It certainly makes one reflect more closely on the relationship of these two complications of pulmonary tuberculosis.

The presence of normal bronchi distal to the stenosis in 2 cases infers that the stenosis was limited in area. One case showed the "obstruction syndrome" and was easily relieved by dilatation.

Seven cases in this group had pneumothorax. Three cases had empyema; in one case the lung reëxpanded well but in the other 2 cases only very slightly. It has been our experience that where an empyema is not present the lung usually reëxpands readily even if a lobar bronchus is stenosed; the affected lobe remains airless, occupies a small area and the more normal lung expands to fill up the excess space, aided possibly by a mediastinal shift. If a stenosis occurs in a main stem bronchus, then the ability of the lung to reëxpand depends upon the condition of the distal lobar bronchi and the presence of atelectasis and fibrosis in the parenchyma.

Bronchograms in inflammatory stenosis: These were made in 26 cases. Normal bronchi were found in 19 cases (73 per cent), obliterative bronchitis in 3 cases (11 per cent) and bronchiectasis in 4 cases (15 per cent). The high figure of normal bronchi is due probably to the short duration of the stenosis. One may expect more abnormal bronchi as the stenosis becomes older.

The 3 cases of obliterative bronchitis changed to bronchiectasis after a period of one year. The "obstruction syndrome" occurred in 3 cases and was relieved by the topical application of adrenalin solution plus gentle dilatation. This group of 26 cases included 20 cases with pneumothorax. Empyema was present in 3 cases and one lung failed to reëxpand.

Bronchoscopic findings in the group without tracheobronchitis: The chief findings in the cases without tuberculous bronchitis were injection and oedema and the presence of secretions.

Nontuberculous injection and oedema occurred both as a localized and as a diffuse process. The swelling was smooth, varied from one examination to another and was easily reduced by topical applications of adrenalin, cocaine, pontocaine, neo-synephrin and benzedrine, leaving an almost normally appearing mucosa. It was usually associated with tenacious and irritating secretion and severe cough. Nontuberculous catarrh is a common finding in pulmonary tuberculosis. Some cases are difficult to differentiate from a tuberculous lesion and need reëxamination and perhaps biopsy. The cases mentioned are those which had more than just a minimum of injection and oedema.

The majority of the cases showed some amount of secretions. This was true also of minimal cases with no cough or expectoration. The secretions may be very tenacious and, upon removal, leave a localized area of reddening and oedema. In our experience, it was felt that the examination of the secretions recovered by bronchoscopy, and the sputum for several days afterwards, was much more valuable than the gastric juice in finding tubercle bacilli.

The incidence of the above findings was as follows: Injection and oedema: 226 cases (43 per cent); localized in 131 cases and not localized in 95 cases. Secretions in the bronchial tree during bronchoscopy: (*a*) moderate amount, 273 cases; (*b*) abundant, 46 cases; total 60 per cent.

Complications of bronchoscopy: We have had the usual complications. Pontocaine in 2 per cent solution has given us excellent results, but we have seen a fair number of reactions due to it, such as nausea, vomiting, dizziness and even syncope. A few cases were made dyspnoeic by it. A postoperative sore throat was common and lasted from several hours to three days. Occasional damage was done to the teeth. We have had no serious complications, such as spontaneous pneumothorax, mediastinal emphysema or atelectasis. In over 2,000 bronchoscopies in this study only one case showed a spread of the disease which might be attributed to the procedure.

For several days afterwards there was an increase in cough and expectoration. Postoperative fever was present in 8 per cent of the cases; it rarely went over 100°F. and was from one to three days' duration. Transient dyspnoea and cyanosis occurring after the bronchosopy was not uncommon, due to the cough, and lasted several seconds to several minutes. Approximately 3 per cent or 4 per cent of the cases showed a drop in a previously existing fever, due apparently to the greater ease of expectoration and improved areation. Quite a number of patients asked for another bronchoscopy because they felt that it facilitated expectoration, lessened cough and improved breathing.

DISCUSSION

The discrepancies in the postmortem incidence reported by various authors is due undoubtedly to the small numbers observed. Our own figure is the same as that found by Louis in 1844 (5). Thousands of cases are necessary to obtain a representative figure. The clinical discrepancies are more easily explained,

since they depend upon the several factors studied and the criteria used in diagnosis. Since biopsies are dangerous and so often uninformative, the clinical incidence depends upon the judgment of the bronchoscopist. The sex factor is considered by some to be of importance. Louis, in 1844, found a greater incidence of bronchitis in men whereas Jenks (6) reported a greater frequency in women. In our own cases, the postmortem group showed a higher percentage in women but the clinical group showed no difference. We doubt that the series published is large enough to have significance on this phase.

Most authors agree that extensive subepithelial disease may be present without ulceration, as pointed out by Ziegler (7) in 1887, that the disease is most common in the smaller bronchi and that there is also an associated nonspecific inflammation present. This latter factor may be variable in intensity and may result in misconceptions in evaluating therapy. With regard to pathogenesis considerable discussion exists. In 1844, Louis stated that, since all of his cases showed the bronchitis to be on the side of the pulmonary cavity, it must be "due to the irritative effects of the sputum." This theory of implantation was more recently substantiated by Bugher, Littig and Culp (8). On the other hand, Reichle and Frost (9) contend that it is due to a lymphangitis and phlebitis of the vessels which pass to the hilum in close proximity to the extracartilaginous glands, that the original source is probably a tuberculous pneumonia of the peribronchial alveoli and that infection occurs by continuity along the submucosa.

In the pathogenesis of this complication several factors are important: (*1*) most cases of bronchitis occur on the side of the more extensive lesion; (*2*) the great majority is associated with positive sputum and cavity; (*3*) the incidence is high in lower lobe disease where sputum drainage is less effective; (*4*) the incidence of bronchitis increases as one approaches a cavity; (*5*) many cases show no peritracheal lesion and the adjacent lymph nodes may be normal; (*6*) clinically, we have seen submucosal lesions progress up the tree to the trachea while the distal portion showed healing; and (*7*) pathologically, submucosal extension is very common. We, therefore, ascribe to both the theory of Louis that the common mode of development is by implantation of tubercle bacilli by sputum to the submucosa and also to the theory of subepithelial extension.

Symptoms are in themselves not pathognomonic of bronchitis, although they may be highly suggestive. If one bronchoscopy reveals no lesion and if symptoms persist, then the examination should be repeated at a later date. Some cases of bronchitis in the small bronchi may then come into the range of endoscopic visibility.

Bugher, Littig and Culp stated that, while evidence of fibrosis was marked, no conclusive proof of a healed ulcer was seen, although some of the localized changes were compatible with healing. Of course, in cases dying from progressive tuberculosis, one cannot expect to see marked examples of healing in any involved organ; yet we have seen several examples of healed ulcers in cases whose original disease was controlled but whose death was caused by progression of the tuberculosis in the other side. Clinically, spontaneous healing has been noted by Myerson (10), Hawkins (11) and McIndoe (1).

The use of collapse therapy in bronchitis is another debatable subject. Samson (12) feels that collapse is of no value. Jenks says that collapse does not control bronchitis in advanced stages even with parenchymal control. Shipman (13) states that collapse therapy may compress diseased bronchi and make the patient worse. On the other hand, Ornstein and Epstein (14) recommend pneumothorax in all cases of bronchitis. Our own views favor the use of collapse since our results show the intimate relationship between the bronchus and the parenchyma, except in cases where one may suspect a resultant bronchial stenosis. The sooner the cavities are closed and the parenchymal lesion controlled the faster will the bronchitis heal, whether collapse is used or bed-rest alone. Some of our best results of bronchitis have followed the use of pneumothorax and thoracoplasty.

The prognosis of cases with bronchitis is considered very poor by Barnwell, Littig and Culp (15) and by Cohen and Wessler (16). Samson feels that it is poor in the ulcerated and stenotic cases but not so serious in those with non-ulcerative lesions. Hawkins does not think that it is too grave because he has seen 17 cases of healed fibrotic stenosis, a high percentage of improvement in pulmonary lesions and some ulcers which healed spontaneously. Our own results show a relatively good prognosis which is only 21 per cent poorer than that obtained in the non-bronchitic cases. The poor prognosis described by some authors may possibly be due to the study of a non-representative group of cases comparable to those in this study which did not do well.

The effects of bronchial occlusion upon cavity closure are only poorly known. Coryllos claimed that all cavities closed only after the bronchi had been occluded. Experimentally, Adams and Vorwald (17) cauterized the bronchi of dogs with pulmonary tuberculosis and produced stenosis which resulted in favorable changes in the lesions and in closure of cavities. We feel that, although some cavities close because of bronchial occulsion, most cases do not follow such a simple course of events and cavities may persist even after bronchial occlusion. However, some cases with bronchitis do show rapid cavity closure and so bronchitis may prove a beneficial factor in the control of the pulmonary lesion. The effects of bronchostenosis upon the formation of bronchiectasis were well described by Haslinger in 1929 (18) and later by Eloesser in 1931 (19). The relationship between an obliterative bronchitis and bronchiectasis needs also to be stressed.

The use of local therapy in bronchitis is one of the most debatable points of the entire subject. Good results are claimed by Warren, Hammond and Tuttle (3) who used 30 per cent silver nitrate and cautery and obtained 59 per cent good results in 57 cases; Sharp and Gorham (2) reported 95 per cent good results in cases with the use of 30 per cent silver nitrate; Packard and Davison (20) used electrocautery in 8 cases and reported improvement in 7 of them. Myerson feels that all active lesions have the ability to heal spontaneously and that local applications may even do harm. Our own experience makes us feel that local treatment is of value, but one must remember that about three-fourths of all cases heal spontaneously if the disease in the parenchyma is controlled. Treatment should be especially applied to the other quarter which does not do well

when the parenchymal lesion is inactivated, or when such complications occur as an undesirable stenosis, an accessible focus of haemorrhage, severe cough, difficulty in expectoration or attacks of dyspnoea.

CONCLUSIONS

1. To study the natural history of tuberculous tracheobronchitis we observed a control group of 125 consecutive autopsies of cases of pulmonary tuberculosis and a clinical group of 622 patients who were bronchoscoped.
2. The features especially stressed were the incidence, course and progress, and prognosis.
3. Tuberculous bronchitis heals spontaneously in about 80 per cent of all patients in whom the parenchymal lesion is controlled and inactivated.
4. Cases with bronchitis show a more severe clinical course and have a poorer prognosis than those with normal bronchi.

CONCLUSIONES

1. Tratando de estudiar la historia natural de la traqueobronquitis tuberculosa, los autores observaron un grupo testigo de 125 autopsias consecutivas de casos de tuberculosis pulmonar, y un grupo clínico de 622 enfermos broncoscopiados.
2. Las características mejor estudiadas fueron la frecuencia, evolución y avance y pronóstico.
3. La bronquitis pulmonar cura espontáneamente en un 80 por ciento de todos los enfermos en que se controla e inactiva la lesión parenquimatosa.
4. Los casos con bronquitis revelan una evolución clínica más grave, y el pronóstico es peor que en los que tienen bronquios normales.

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POSTBRONCHOSCOPIC REACTIONS IN PULMONARY TUBERCULOSIS[1]

DAVID B. RADNER

With the renewal of interest in tuberculous tracheobronchitis stemming from the work of Eloesser (1) and increasing in momentum following the reports of Samson (2), Barnwell, Littig and Culp (3), Kernan (4), Warren, Hammond and Tuttle (5) and Myerson (6), considerable information pertaining to this subject has accumulated. As the knowledge grew, indications increased and benefits derived swelled to such a point that recent reports (7, 8) have appeared suggesting the advisability of doing routine bronchoscopic examinations on all sanatorium admissions. Others have limited the bronchoscopic routine to all cases amenable to collapse therapy.

Not unmindful of the significant rôle this information has played in the improvement and appraisal of our collapse therapy program, it is nevertheless a fact that bronchoscopy in the tuberculous was at first looked upon with a certain amount of misgiving by the phthisiologists. In the light of our knowledge concerning the disease, this was understandable. However, due largely to the efforts of Kernan (9), Clerf (10) and Myerson (11), pulmonary tuberculosis was removed from the list of contraindications to bronchoscopy. The contraindications: acute laryngeal tuberculosis, recent haemoptysis and far advanced disease with toxaemia and cachexia have been accepted by most operators. As a result, the procedure gained favor with physicians dealing with tuberculosis and numerous interesting reports of cases treated followed.

In 1939 McIndoe, Steele and Samson (12), in an effort to determine whether the examination had any deleterious effect on pulmonary tuberculosis, studied a series of 272 patients. That report represents the only attempt to go beyond an impression gained by many operators. They concluded that routine bronchoscopy was not necessary and actually offered little information over that obtained from the bronchoscopic examination of patients who demonstrated the symptoms usually associated with tracheobronchial disease. Their study included 4 cases showing an increase in pulmonary disease, 49 patients demonstrating some febrile reaction and 45 patients exhibiting temporary changes in the larynx following bronchoscopy. However, they felt there was no proof that the increase noted on roentgenogram was necessarily the result of bronchoscopy.

At the present time, indications for bronchoscopy in pulmonary tuberculosis may be summarized as follows:

1: Intermittent or unexplained atelectasis.
2: Wheeze.
3: Persistent positive sputum which is inconsistent with the clinical and roentgenological course.
4: Marked variation in the daily sputum volume.
5: Unexplained haemoptysis.

[1] From The Leahi Hospital, Honolulu, Hawaii.

6: As routine procedure prior to thoracoplasty.
7: To determine source of positive sputum in the absence of roentgenologically demonstrable parenchymal lesions.

For more than five years we have adhered, with few exceptions, to the indications outlined above and, because of several cases where clinical and roentgenological changes were manifest which did not appear entirely coincidental, the following study was suggested. Over a period of one year, a study of 97 patients bronchoscoped a total of 180 times was made to determine what effect, if any, bronchoscopy had on the course of pulmonary tuberculosis. Serial roentgenograms and clinical records were examined for evidence of postbronchoscopic reactions. This information was correlated with the presence of acid-fast organisms in the sputum, presence of cavitation and presence of tracheobronchial lesions. Of the 97 patients studied, 53, examined a total of 73 times, demonstrated no significant change in the temperature curve, nor evidence of deviation from the expected course of the disease as viewed by serial roentgenograms. The remainder, 44 patients, bronchoscoped a total of 110 times, yielded significant and consistent febrile or roentgenological changes. Before entering upon a discussion of these findings, it is appropriate that a description be given of the method of examination used.

TECHNIQUE

With only two exceptions, all the patients received a dose of barbiturate, such as amytal, from sixty to ninety minutes prior to bronchoscopy. In several cases where such was deemed inadequate, it was supplemented with a small dose of morphine sulphate ($\frac{1}{4}$ or $\frac{1}{3}$ grain) hypodermically, approximately thirty to forty-five minutes before bronchoscopy. Local anaesthesia was obtained by the use of either 5 per cent or 10 per cent solution of larocain or 2 per cent solution of pontocaine and included one to two cc. instilled intratracheally. Bronchoscopy was performed using either the Haslinger or standard Jackson instrument and the duration of the examination ranged between three and five minutes. Within the tracheobronchial tree, topical applications were limited to 25 per cent solution of silver nitrate or 10 per cent solution of cocaine with adrenalin (1:1,000 M iii per cc.) using Jackson sponges partially dried. A normal bronchus was avoided after examination or treatment of a diseased bronchus. Biopsy was not done in any case in this series.

The following indications were responsible for the bronchoscopic examinations:

Prior to thoracoplasty	34
Unexplained atelectasis	11
Wheeze	14
Persistent positive sputum	23
Source of positive sputum	9
Unexplained haemoptysis	4
Lung abscess with pulmonary tuberculosis	1
Old lesion right main bronchus	1
	97

POSTBRONCHOSCOPIC FINDINGS

Febrile response: In the report by McIndoe, Steele and Samson (12) the temperature was studied for one week before and one week after bronchoscopy.

They reported 50 cases which showed a temporary rise in temperature under the conditions of their study. Of the 183 bronchoscopies in the present study, a febrile response appearing within seventy-two hours was encountered in 18 cases. We feel, as they do, that this probably represents a nonspecific reaction and is of no significance. The temperature rise ranged from one to three degrees and with very few exceptions subsided within seven days. When, however, the temperature curve is followed over a longer period of time, a secondary rise in temperature is noted not infrequently which has a fairly constant time of onset. This appeared following 26 bronchoscopic examinations and in almost 75 per cent of these cases it began between the tenth and sixteenth postoperative day. There were undoubtedly more responses of this type that could not be included because of an irregular febrile course preceding bronchoscopy, making the curve inconclusive. The 26 instances listed represent only the unquestioned rises in temperature. Patients with pulmonary tuberculosis undoubtedly demonstrate periods of fever but it is beyond the province of coincidence to find this number all falling into a well defined time interval. The secondary rise cannot be looked upon as insignificant and probably represents the constitutional response to some specific change in the respiratory tract. Many of the patients complained of headache, anorexia and increased cough during this period. Further, this period was often accompanied by manifest changes in the roentgenogram and the febrile period often extended into months before subsiding. The rise in temperature varied between one and three degrees, lasting, on an average, between two and three weeks. This secondary rise, if due to the formation of new or reactivation of old foci, takes on particular significance in the cases examined prior to thoracoplasty. It is also of importance in deciding upon the interval for treatment in cases where tracheobronchial lesions exist.

Roentgenological changes: In addition to the 4 cases cited by McIndoe, Steele and Samson (12) in which an increase in disease was noted following bronchoscopy, Warren, Hammond and Tuttle (5) reported 2 cases in their series, and Hawkins (13) reported one case developing spread following bronchoscopy. Clerf and Putney (14) quote a report by Kernan and Cracovaner in which 2 cases had spread of infection following bronchoscopy. Jenks (15) in a more recent article discussed this question and mentioned another 2 instances of spread following bronchoscopy brought to his attention by Dr. J. B. Amberson who thought the occurrence might have been more than mere coincidence.

In the selection of these cases none were included that showed progression or extension of disease prior to bronchoscopy. Whether any of the progressive cases were influenced by bronchoscopy cannot be demonstrated as the preoperative febrile and X-ray course eliminated them from this study. Some of the cases exhibited a low-grade fever prior to bronchoscopy which showed no material alteration following examination, and these were also excluded from the group showing definite febrile reactions.

In the present series, definite roentgenological changes were noted in 26 instances. In 5, atelectasis of a lobe or entire lung followed bronchoscopy. In 21, the change noted took the form of a fresh area of infiltration either in the

homolateral or contralateral lung. In general these areas behaved as new exudative foci, taking from two to four months to clear. With one exception all did clear spontaneously. The greatest number showed minimal infiltrative lesions, 2 showing increase in the size of the cavity with definite increase in the perifocal reaction about the cavity. These minimal spreads appeared, as a rule, in the third to fifth week following bronchoscopy and were noted either during the period of secondary fever or closely following it. In approximately one-third of the instances, either the extension of disease was not accompanied by fever or the fever curve was not followed by definite evidence of progression on the X-ray films available for study. However, in tuberculosis it is not a rare occurrence to find slight progression of disease without fever. In the 5 cases of atelectasis, all were found to have tracheobronchial disease and it is reasonable to assume that the inflammation and oedema resulting from examination with a rigid metal tube, superimposed upon a previously diseased bronchial wall, might have been sufficient to occlude a partially stenosed lumen. Likewise, atelectasis is frequently a spontaneous occurrence in patients with advanced tracheobronchial disease. In 1937, Barnwell, Littig and Culp (3), in their exhaustive study on the pathogenesis of tracheobronchial disease, made special reference to this point.

Significance of fever and roentgenological changes: Without attaching any importance to the immediate postoperative rise in temperature, the 26 instances of secondary fever, accompanied by roentgenological and constitutional reactions in many, cannot be ignored. While it is true that these changes were not serious (with one exception), it is also true that more intelligent management of the case is possible if they are taken into account. Further extension of disease may result from the reintroduction of the bronchoscope during the height of such a reaction. Bronchoscopy followed within a week by thoracoplasty may lead to false interpretation as to the cause of spread seen postoperatively. In addition the added trauma of surgery is apt to intensify postbronchoscopic spread. For these reasons it has been our policy for the past year to allow two and preferably three weeks between bronchoscopy and thoracoplasty. The X-ray film of the chest is repeated prior to chest surgery and if no fever or roentgenological evidence of spread is present, no contraindication to surgery is assumed to be present. Under such a regimen, 167 stages of thoracoplasty have been performed on 45 patients with no instance of postoperative spread. Likewise, it has been our impression that prolonging the interval between endoscopic treatment to eight weeks has resulted in fewer cases of ulceration developing while under treatment.

The following are illustrative cases:

Case 1: E. A., a thirty-two year old Chinese-Hawaiian male, admitted to the hospital April 29, 1940 for the third time. The history of pulmonary disease dated back to 1931. A first-stage thoracoplasty with removal of the first two ribs on the right had been done in 1936. The patient refused further thoracoplasty stages and on the third admission X-ray films revealed an old, moderately thick fibrous walled cavity (2 cm.) at the level of the fifth posterior rib on the right and an old minimal productive infiltration in the left apex. The sputum was positive for acid-fast bacilli. After a period of observation, bronchos-

copy was done May 23, 1940 with completion of thoracoplasty to follow if no contra-indication was found. Examination revealed diffuse hyperaemia of the left main bronchus but no ulceration. On the ninth postbronchoscopic day, the patient's temperature rose to 99.4°F. reaching 101°F. on the tenth and eleventh days, returning to normal on the thirteenth day. Roentgenogram taken on the twelfth day revealed a marked increase in the size of the cavity with a definite increase in perifocal reaction about it. During this period the patient complained of headache and increased cough. After a three-month period of bed-rest, the spread subsided and thoracoplasty was resumed September 18, 1940, with an uneventful course.

Case 2: B. S., a seventeen year old Japanese male, admitted September 28, 1933 with a history of pulmonary tuberculosis of one year's duration. Left artificial pneumothorax had failed prior to admission. Because of positive sputum and a bilateral lesion, artificial pneumothorax was induced on the right side in 1937 with the hope that thoracoplasty on the left could eventually be accomplished. Thoracoplasty was postponed after the patient developed gastro-intestinal symptoms, diagnosed as tuberculous enteritis by X-ray study. The patient showed slow improvement and in 1940 was clinically well enough to be reconsidered for thoracoplasty. The right lung had been reëxpanded and the left lung showed a well stabilized fibrocaseous lesion in the apex. Bronchoscopy was done July 10, 1940 and distortion of the trachea and left main bronchus, but no inflammatory process, was found. There was no rise in temperature until the sixteenth postbronchoscopic day when it rose to 99.4°F. and continued until the twenty-seventh day when it reached 102.2°F. The temperature gradually returned to normal after a febrile period lasting thirty-one days. Roentgenogram taken on the twenty-fifth day revealed a definite spread of the disease on the left at the level of the second interspace and second rib. During this interval the patient complained of headache, malaise, anorexia and increased cough. Thoracoplasty was postponed until March, 1941 when the lesion appeared stabilized. The subsequent course was uneventful.

Case 3: B. K., Japanese female, aged twenty-one, admitted September 12, 1938 with a history of illness dating two years. On admission the roentgenogram of the chest revealed an exudative-productive infiltration throughout both upper lobes. The sputum was positive for acid-fast bacilli. Artificial pneumothorax was induced on the left September 20, 1938, followed by left intrapleural pneumonolysis March 16, 1939. Bronchoscopy was recommended because of persistently positive sputum and an ulcero-granulomatous lesion was found in the left main bronchus. Left phrenic paralysis which had been contemplated was, of course, withheld and the patient was treated endoscopically with 25 per cent solution of silver nitrate. Five weeks following bronchoscopy on November 8, 1939 roentgenograms revealed increased infiltration off the left hilum. Subsequently the patient appeared to improve clinically and bronchoscopically until twenty days after a bronchoscopy done on October 14, 1940. At that time the mucous membrane of the left main bronchus showed some chronic thickening and there was partial stenosis of the lumen. No ulceration was present and only a small amount of secretion was aspirated. No local medication was applied. On the twentieth day following this bronchoscopy, the patient's temperature rose to 99.2°F. and remained between 99.2° and 99.4°F. until the twenty-sixth day when it reached 102°F. It remained above 102°F. for six days then began to drop gradually, reaching normal after a total of twelve days of elevation. During this period the patient complained of headache, generalized neuro-muscular pains, increased cough and left chest pain. Roentgenograms taken October 14,

1940 and November 28, 1940 revealed a marked increase in fresh exudative infiltration in the left lung. This had cleared and resorbed by February, 1941. No further bronchoscopies were done on this patient.

DISCUSSION

When these cases of postbronchoscopic spread came to our attention, an explanation as to the underlying cause and possible prevention was sought. All cases studied had positive sputum, many demonstrating open cavities. All but 4 had some tracheobronchial disease. Direct implantation was possible but unlikely, since in many instances contralateral spread occurred where no contact with the contralateral bronchus was made. Excessive or severe coughing following bronchoscopy was then considered as a possible factor in producing trauma to the diseased area or resulting in possible "in-coughing" of bacillus-laden secretions. This seemed unlikely because the severe postbronchoscopic cough was not a constant factor and, when it did occur, lasted only a very short time. It is conceivable that repetition of bronchoscopy may play a rôle in the production of spread. Yet of the 21 cases developing spread following bronchoscopy, 8 were examined only once, the remainder from two to five times. Others under treatment for tracheobronchial lesions were bronchoscoped four to six times with no evidence of spread. It is our impression that the most likely explanation rests on the abolishment of the cough reflex and disturbance of ciliary action.

Jenks (15) discussed a suggestion of Doctor Amberson that in abolishing the cough reflex anaesthesia might be a significant factor. He counters this suggestion with the statement that cough following removal of the bronchoscope, as well as the short period during which the cough reflex is abolished, makes it seem logical that the likelihood of spread of disease following bronchoscopy is less than before. Nevertheless, he suggests that in order to minimize the risk, the patient be instructed to lie on the affected side until the cough reflex is regained. While this will minimize the danger of contralateral spread, it will also enhance the chance of homolateral spread. It would seem more logical to disturb the cough reflex as little as possible by readjusting our technique of anaesthesia. Tracheal and bronchial anaesthesia superimposed upon basal anaesthesia, such as is obtained by the barbiturates, usually results in a moderately deep sleep, relatively free of cough, lasting from four to eight hours or longer. While the tracheobronchial tree may be relatively free from secretions following bronchoscopy, two hours may be sufficient time for accumulation to occur. The absence or diminution in the cough reflex, plus the absence or retardation of ciliary action, might account for the spread of the organisms from one bronchus to another. The lavage effect of 2 cc. of anaesthetic solution in itself may be insufficient to explain the findings but may act as a contributing factor. For the past year, therefore, it has been our practice to use the shorter acting barbiturates (seconal, nembutal) and avoid tracheal anaesthesia, except where absolutely necessary to carry out the examination or treatment. In no case do we instill 1.0 to 2.0 cc. of the local anaesthetic intratracheally as formerly. When an anaesthetic is

necessary, it is applied topically to the particular area, usually the carina. The dropping in of an anaesthetic solution to spread over both main bronchi and/or its branches is in reality unnecessary though it does simplify the work for the operator. Postoperatively patients are urged to cough at frequent intervals. Carbon dioxide and oxygen inhalations, as they are used postoperatively in thoracic surgery, are not desirable following bronchoscopy since the excessive coughing and expectoration induced by the gas is not beneficial in tracheobronchial disease. While as yet no detailed study has been made of the cases bronchoscoped since this change in technique, we have been ever conscious of this possibility in our staff conferences and only one case of spread has been reported by the resident staff. This followed an endoscopic treatment of a partially stenosed bronchus leading to an atelectatic lobe. The result was a typical febrile response accompanied by marked bronchogenic spread to the remainder of the same lung.

SUMMARY AND CONCLUSIONS

The subject of tuberculous tracheobronchitis is of tremendous interest to the phthisiologist and thoracic surgeon. The trend toward routine bronchoscopic examination of all patients admitted to the sanatorium is not without its disadvantages. Limitation of bronchoscopy to the indications described will suffice to take care of almost all cases requiring treatment. Eleven cases have been collected from the American literature in which spread of disease following bronchoscopy is mentioned. Not in all instances did the authors feel definitely that bronchoscopy was directly responsible for the spread.

In a study of 183 bronchoscopic examinations made on patients with pulmonary tuberculosis the following findings were obtained, indicating that bronchoscopy is not an innocent procedure:

1. Eighteen bronchoscopic examinations were followed by immediate postbronchoscopic fever to which little significance can be attached.
2. Twenty-six bronchoscopic examinations were followed by a secondary rise in temperature, appearing between the tenth and sixteenth postbronchoscopic day, lasting fourteen to twenty-one days.
3. Twenty-one bronchoscopies were followed by minimal infiltrative spread as seen on roentgen films.
4. Five bronchoscopic examinations were followed by atelectasis of a lobe or lung.

In this series, the number of patients who developed fever and spread of lesions following bronchoscopy is beyond explanation by coincidence.

As a result of these findings it is suggested that:

1. Patients bronchoscoped prior to thoracoplasty should have their examination preferably three weeks in advance with a new roentgen film of the chest before surgery. This will eliminate some of the postoperative spreads that may be seen following thoracoplasty which are unjustifiably attributed to surgery.
2. The interval between bronchoscopic examination or treatments should not be less than six or eight weeks to allow for subsidence of any reaction resulting from previous treatments.

3. The disturbance of the cough reflex is very likely associated with the febrile reaction and extension of disease reported above. To minimize this, prebronchoscopic medication should preferably be limited to short acting drugs and intratracheal anaesthesia avoided whenever possible.

SUMARIO Y CONCLUSIONES

El tema de la traqueobronquitis tuberculosa reviste enorme interés tanto para el tisiólogo como para el cirujano del tórax. La tendencia actual de ejecutar exámenes broncoscópicos sistemáticos en todos los enfermos recibidos en el sanatorio no deja de tener sus inconvenientes, y la limitación de la broncoscopia a las indicaciones aquí descritas bastará para atender a casi todos los casos que exigen tratamiento. De la literatura estadounidense se han recogido once casos, en los cuales se menciona propagación de la dolencia consecutivamente a la broncoscopia, aunque no en todos los casos se sentían los autores seguros de que la última fuera la causa directa de la difusión.

En un estudio de 183 exámenes broncoscópicos realizados en casos de tuberculosis pulmonar se obtuvieron los siguientes hallazgos indicativos de que la broncoscopia no constituye un procedimiento inocuo:

1. Dieciocho exámenes broncoscópicos fueron seguidos inmediatamente de fiebre, a lo cual no puede concedérsele mayor importancia.

2. Veintiséis exámenes broncoscópicos fueron seguidos de una hipertermia secundaria que duró de catorce a veintiún días, y, que por lo general se presentó entre el décimo y el décimosexto día consecutivo a la broncoscopia.

3. Según revelaron las películas radiográficas, veintiuna broncoscopias fueron seguidas de una propagación infiltrante mínima.

4. Cinco exámenes broncoscópicos fueron seguidos de atelectasia de un lóbulo o un pulmón.

En esta serie no cabe explicar por mera coincidencia el número de enfermos que manifestaron fiebre y propagación de las lesiones consecutivamente a la broncoscopia.

Como resultado de estos hallazgos, propónese que:

1. En los enfermos examinados antes de la toracoplastia se realice la broncoscopia de preferencia tres semanas antes, acompañándola de una nueva película radiográfica del tórax antes de operar, lo cual eliminará algunas de las propagaciones postoperatorias observadas después de la toracoplastia, y que se atribuyen injustificadamente a la operación.

2. El intervalo entre el examen y el tratamiento broncoscópico no debe ser menor de seis a ocho semanas, a fin de permitir la desaparición de toda reacción debida a los tratamientos anteriores.

3. El trastorno del reflejo de la tos con toda probabilidad se asocia con la reacción febril y propagación mencionadas previamente. A fin de aminorar esto, la medicación prebroncoscópica debe de preferencia limitarse a drogas de acción breve, evitando siempre que sea posible la anestesia intratraqueal.

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PULMONARY CALCIFICATION AND TUBERCULIN SENSITIVITY AMONG CHILDREN IN WILLIAMSON COUNTY, TENNESSEE[1]

R. S. GASS, E. F. HARRISON, RUTH R. PUFFER, H. C. STEWART AND W. C. WILLIAMS

In 1937, a radiographic study (1) of school children in Williamson County revealed a high frequency of calcified lesions in the lung fields and tracheobronchial lymph nodes. These lesions were found to be somewhat more prevalent in white than in colored children. The most remarkable finding, in view of the fact that such calcification is usually considered to be tuberculous, was that the proportion of children showing these lesions was only slightly higher among the tuberculin-positive than among the tuberculin-negative children.

These observations have been confirmed by similar studies in 1939 and in 1941. The former (2) has been reported. Similar techniques, including the Mantoux test with the identical lot of Old Tuberculin, were used for all three studies.

Following the 1941 survey, a complete restudy was made of all X-ray films of children who had been included in two or three of the studies. These serial films have permitted decisions regarding calcification in doubtful cases. It is possible that there were children who had small calcified lesions which were not detected even on two or three serial films. The use of serial films, however, has made the diagnosis of calcification highly dependable.

The purposes of this report are threefold, namely: (*1*) to present an analysis of the frequency of calcification as determined by serial X-ray examinations; (*2*) to discuss certain characteristics of school children who have acquired demonstrable calcification between examinations; (*3*) to study the relationship between calcification and sensitivity to tuberculin.

ANALYSIS OF FREQUENCY OF CALCIFICATION AS DETERMINED BY SERIAL FILMS

In all, 935 white and 232 colored school children were examined in two of the school studies and some of these children were examined in all three studies. The numbers of white and colored school children examined, the years of examination and the prevalence of calcification are shown in table 1.

The net result of review of serial radiograms has been to increase materially the proportion with calcification. At least 83 per cent of the white and 72 per cent of colored school children have calcified lesions in the lungs or tracheobronchial lymph nodes.

The prevalence of calcification in these school children has been studied according to age, sex and color and the data are shown in table 2.

The consistency of the percentages of children with calcification in the three age groups was remarkable and it should be noted that 79.6 per cent of the white

[1] From the Tennessee Department of Public Health. This investigation was made possible by the financial support of the International Health Division of the Rockefeller Foundation.

and 66.7 per cent of the colored children in the youngest age group studied had demonstrable calcification. Both males and females were found to have approximately the same frequencies.

The amount of calcification (extensive, moderate and limited) is shown in table 3 by age group. This calcification may have been noted either in the

TABLE 1

Number of school children with serial films with years of examinations and prevalence of calcification on last examination according to final interpretation, by color

YEARS OF EXAMINATION	WHITE			COLORED		
	Total examined	Calcification		Total examined	Calcification	
		Number	Per cent		Number	Per cent
Total	935	773	82.7	232	168	72.4
1937 and 1939	281	227	80.8	77	54	70.1
1939 and 1941	291	232	79.7	64	46	71.9
1937 and 1941	66	54	81.8	8	6	75.0
1937, 1939 and 1941	297	260	87.5	83	62	74.7

TABLE 2

Prevalence of calcification on last examination by age group, by color and sex of 1,167 school children with serial films

AGE GROUP	TOTAL			MALE			FEMALE		
	Total	Calcification		Total	Calcification		Total	Calcification	
		Number	Per cent		Number	Per cent		Number	Per cent
White									
Total	935	773	82.7	447	366	81.9	488	407	83.4
7–9 years	93	74	79.6	40	26	65.0	53	48	90.6
10–14 years	450	374	83.1	233	196	84.1	217	178	82.0
15–19 years	392	325	82.9	174	144	82.8	218	181	83.0
Colored									
Total	232	168	72.4	104	76	73.1	128	92	71.9
7–9 years	33	22	66.7	19	15	78.9	14	7	50.0
10–14 years	125	94	75.2	62	43	69.4	63	51	81.0
15–19 years	74	52	70.3	23	18	78.3	51	34	66.7

parenchyma of the lungs or tracheobronchial lymph nodes or both. The extent was classified as follows:

Extensive: One large mass of calcification of at least 1.5 cm. in diameter or multiple foci in the parenchyma and/or tracheobronchial lymph nodes.

Moderate: One area of calcification between 1.5 and 0.5 cm. in diameter or two or three smaller areas.

Limited: One or more calcified areas less extensive than classified as moderate.

The proportion of the children with limited calcification tended to increase with age while the proportion with extensive calcification was smaller for the older children than for the younger ones. It is more difficult to read calcification in the root region in the older age group due to the thickness of the chest and increased root markings. These factors may be in part responsible for the differences in the extent of calcification. Although there may be some absorption

TABLE 3

Extent of calcification by age group and by color of 1,167 school children with serial films

AGE GROUP	TOTAL		NEGATIVE		CALCIFICATION					
					Limited		Moderate		Extensive	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
White										
Total	935	100.0	162	17.3	164	17.5	499	53.4	110	11.8
7-9 years	93	100.0	19	20.4	10	10.8	49	52.7	15	16.1
10-14 years	450	100.0	76	16.9	79	17.6	235	52.2	60	13.3
15-19 years	392	99.9	67	17.1	75	19.1	215	54.8	35	8.9
Colored										
Total	232	100.1	64	27.6	38	16.4	99	42.7	31	13.4
7-9 years	33	100.0	11	33.3	5	15.2	11	33.3	6	18.2
10-14 years	125	100.0	31	24.8	21	16.8	54	43.2	19	15.2
15-19 years	74	99.9	22	29.7	12	16.2	34	45.9	6	8.1

TABLE 4

Prevalence of calcification on last examination by schools of 1,167 school children with serial films

	TOTAL EXAMINED	CALCIFICATION	
		Number	Per cent
Total white schools	935	773	82.7
Franklin	626	522	83.4
Hillsboro, Triangle and Thompson Station	132	103	78.0
College Grove, Triune and Nolensville	177	148	83.6
Total colored schools	232	168	72.4

of calcium deposits with age, additional observations are desirable to determine this fact.

In the study of calcification, the possibility of a geographical distribution in the county has been considered and the data are shown in table 4 for the three areas in which the schools were located.

One of the school areas was Franklin, the county seat with a population of

4,120. The rest of the schools were scattered throughout the rural sections of the county. No significant geographical variation was observed. Therefore, calcification appears to be caused by conditions which are widely and uniformly spread throughout the county.

Broader geographical differences have been brought out by Lumsden and Dearing (3) in discussing the findings in areas in which limestone and chert formations are found.

NUMBER OF SCHOOL CHILDREN WHO ACQUIRED CALCIFICATION

In the review of the serial films, 27 white and 4 colored children who had no evidence of calcification on first examination were found to have acquired calcification prior to the last serial films. "Addition of calcification" is used to denote acquirement of calcification of children who were negative on first examination and who were found to have demonstrable calcification on a later film. The data regarding such addition of calcification for white and colored school children

TABLE 5

Addition of calcification among school children negative on first examination, by color and years of examination

YEARS OF EXAMINATION	WHITE			COLORED		
	Total negative	Addition of calcification		Total negative	Addition of calcification	
		Number	Per cent		Number	Per cent
Total	189	27	14	68	4	6
1937 and 1939	56	2	4	25	2	8
1939 and 1941	63	4	6	18	—	—
1937 and 1941	19	7	37	2	—	—
1937, 1939 and 1941	51	14	27	23	2	9

according to year of examination are given in table 5. These examinations were made at two-year intervals in the first few months of the year in 1937, 1939 and 1941. However, in 1941 one school was completed in November of the year.

Of the 935 white and 232 colored children, 189 white and 68 colored had no calcification on first examination. Of the white, 14 per cent and of the colored, 6 per cent were found to have acquired lesions between X-ray examinations. In considering the four different groups, it should be pointed out that when the longer period had elapsed, four years, a larger proportion of these children negative on first examination were found to have acquired calcification. An example of one white school child who acquired calcification between the first and second examination is given as an illustration. On first examination, there was no evidence of calcified lesions, although infiltration was noted in the right cardiohepatic angle. On second examination, two years later, a definite calcified nodule, 0.5 cm. in diameter, had formed at the level of the inner portion of the fourth anterior interspace about 3 cm. from the mediastinal shadow and 3.5

cm. above the diaphragm. Some infiltration remained in this area surrounding the calcified nodule. The nodule remained the same on the third examination two years later.

A few children examined in a nursery school in 1937 were included in this group of children with serial films. Thus, these children were very young when the first and subsequent examinations were made.

The data, divided according to age group at the time of first examination, are given in table 6.

It is evident from these figures that children in Williamson County acquire pulmonary calcification at a very early age. None of the school children fifteen to nineteen years of age at first examination and without calcification at that time were found to have acquired calcification during the period of observation. This indicates the need of a more intensive study of the preschool age group to learn the underlying factors causing pulmonary calcification.

TABLE 6

Number of school children without calcification on first examination who acquired calcification, according to age at time of first examination, by color

AGE GROUP	WHITE			COLORED		
	Total negative	Addition of calcification		Total negative	Addition of calcification	
		Number	Per cent		Number	Per cent
Total	189	27	14	68	4	6
Under 5 years	6	5	83	—	—	—
5–9 years	90	17	19	27	2	7
10–14 years	66	5	8	33	2	6
15–19 years	37	—	—	8	—	—

RELATIONSHIP BETWEEN CALCIFICATION AND TUBERCULIN SENSITIVITY

The final X-ray interpretations of the serial films have been studied in relation to the tuberculin reaction at the time of the last X-ray examination and the results are shown in table 7.

The tuberculin tests were completed for 881 white and 225 colored school children. The percentage of children with positive tuberculin reactions to 0.01 mg. of OT tended to increase with the amount of calcification. Among the white children with extensive calcification, 15.7 per cent reacted to 0.01 mg., while among those without calcification but 5.9 per cent reacted to 0.01 mg. Among the colored children the same tendency was noted.

When the percentages of those with calcification who reacted to tuberculin were compared with those without calcification, the significance of the small dose (0.01 mg.) was evident. Among the white 12.5 per cent of those with calcification reacted to 0.01 mg. while only 5.9 per cent of those without calcification reacted. Among the colored the percentages were 23.3 and 9.7 respectively. There was no definite relation between calcification and reaction to the larger

dose of 1.0 mg. These findings indicate that sensitivity to tuberculin as measured by the small dose of OT was found more frequently among those with calcification than among those without calcification.

The tuberculin reactions of school children who acquired calcification have been studied and the results of first and last tests for the 27 white school children are shown in table 8.

TABLE 7

Tuberculin reactions of school children at time of last X-ray examination according to final interpretation, by color

TUBERCULIN REACTION	TOTAL		NEGATIVE		CALCIFICATION					
					Limited		Moderate		Extensive	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
White										
Total	881	100.0	152	100.0	154	100.0	473	100.0	102	100.0
Positive to 0.01 mg.	100	11.4	9	5.9	20	13.0	55	11.6	16	15.7
Positive to 1.0 mg.	255	28.9	50	32.9	38	24.7	140	29.6	27	26.5
Negative	526	59.7	93	61.2	96	62.3	278	58.8	59	57.8
Colored										
Total	225	100.1	62	100.0	36	100.0	96	100.0	31	100.1
Positive to 0.01 mg.	44	19.6	6	9.7	5	13.9	22	22.9	11	35.5
Positive to 1.0 mg.	58	25.8	16	25.8	8	22.2	32	33.3	2	6.5
Negative	123	54.7	40	64.5	23	63.9	42	43.8	18	58.1

TABLE 8

First and last tuberculin reactions for 27 white school children who acquired calcification during study

FIRST TUBERCULIN READING	LAST TUBERCULIN READING				
	Total	Positive to 0.01 mg.	Positive to 1.0 mg.	Negative	Not completed
Total	27	5	5	15	2
Positive to 0.01 mg	2	2	—	—	—
Positive to 1.0 mg	9	2	2	4	1
Negative	14	1	3	9	1
Not completed	2	—	—	2	—

Of these 27 children, 2 were positive to 0.01 mg. on first tuberculin test when they were found to have no pulmonary calcification and these 2 remained positive to 0.01 mg. Nine reacted to 1.0 mg. on first test and 2 of these had become positive to 0.01 mg., 2 remained positive to 1.0 mg., 4 had become negative and the final test was not completed in one. Only one of the 14 negative on first test had become positive to 0.01 mg. and 3 had become positive to 1.0 mg. There-

fore, it appears that many of these children acquire calcification without showing tuberculin sensitivity. It is possible, however, that regression has taken place and that tuberculin tests at shorter intervals might have revealed sensitivity to tuberculin.

TABLE 9

Results of first and last tuberculin tests on 27 white school children who acquired calcification and 162 who did not acquire calcification

TUBERCULIN REACTION	SCHOOL CHILDREN WHO ACQUIRED CALCIFICATION				SCHOOL CHILDREN WHOSE X-RAY FILMS REMAINED NEGATIVE			
	First tuberculin		Last tuberculin		First tuberculin		Last tuberculin	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Total	27	99	27	101	162	100	162	100
Positive to 0.01 mg	2	7	5	19	5	3	9	6
Positive to 1.0 mg	9	33	5	19	51	31	50	31
Negative	14	52	15	56	103	64	93	57
Not completed	2	7	2	7	3	2	10	6

TABLE 10

Results of three series of tuberculin tests of school children with X-ray examinations in 1937, 1939 and 1941, according to final interpretation, by color

TUBERCULIN REACTION TO 0.01 MG.	TOTAL		NEGATIVE		CALCIFICATION					
					Limited		Moderate		Extensive	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
White										
Total	296	100	36	100	58	100	174	100	28	100
Positive—3 times	17	6	1	3	2	3	12	7	2	7
Positive—2 times	8	3	—	—	1	2	3	2	4	14
Positive—1 time	22	7	3	8	5	9	13	7	1	4
Negative—3 times	249	84	32	89	50	86	146	84	21	75
Colored										
Total	77	100	20	100	6	100	41	100	10	100
Positive—3 times	9	12	—	—	—	—	4	10	5	50
Positive—2 times	4	5	1	5	—	—	2	5	1	10
Positive—1 time	4	5	1	5	—	—	3	7	—	—
Negative—3 times	60	78	18	90	6	100	32	78	4	40

The results of the tests of the 27 children who acquired calcification and of the 162 children who did not acquire demonstrable calcification are shown in table 9.

Of the 27 white children who acquired calcification, 5, or 19 per cent, were positive to 0.01 mg. on the last tuberculin tests, while of the 162 white children who remained negative, 9, or 6 per cent, were positive to 0.01 mg. Although the numbers are small, there is a suggestion that the children who acquired

calcification had a somewhat greater tendency to acquire sensitivity to tuberculin than those whose X-ray films did not show calcification.

The final interpretations of serial films for children with three films, that is, for children examined in 1937, 1939 and 1941, have been related to the reaction to 0.01 mg. of tuberculin on three occasions at two-year intervals as shown in table 10.

Of the children with extensive calcification who had three tuberculin tests, 25 per cent were positive to 0.01 mg. on one or more of the tests, while only 11 per cent of those without calcification reacted to 0.01 mg. on one or more occasions. Among the colored, also, of 10 with extensive calcification 6 were sensitive to 0.01 mg. on one or more occasions. These findings indicate some degree of positive association between sensitivity to small doses of tuberculin and amount of pulmonary calcification.

SUMMARY

1. Restudy of serial X-ray films of 1,167 school children who were examined in two or all of the three school surveys in 1937, 1939 and 1941 revealed that 83 per cent of the white and 72 per cent of the colored had pulmonary calcification. Prevalence of these lesions was approximately as high in children seven to nine years of age as in the older children. Lesions were about equally frequent in males and females. No significant differences in prevalence of calcification were found in different areas of the county.

2. Twenty-seven white and 4 colored children were found to have acquired pulmonary calcification between examinations two or four years apart. Those acquiring calcification were all under fifteen years of age. This finding and the high prevalence at seven to nine years of age indicate that children in Williamson County acquired pulmonary calcification at a very early age. Many of the children acquiring calcification failed to show tuberculin sensitivity.

3. On study of pulmonary calcification in relation to tuberculin sensitivity it appeared that sensitivity to tuberculin as measured by 0.01 mg. of OT was found more frequently among those with calcification than among those without calcification.

SUMARIO

1. Al estudiar de nuevo las películas roentgenológicas seriadas de 1,167 escolares examinados en dos o tres censos de los escolares de 1937, 1939 y 1941, descubrióse que 83 por ciento de los blancos y 72 por ciento de los de color revelaban calcificación pulmonar. La frecuencia de estas lesiones fué aproximadamente igual en los niños de 7 a 9 años que en los mayores. Las lesiones acusaron una frecuencia casi igual en los varones que en las mujeres. No se descubrieron diferencias significativas en la frecuencia de la calcificación en las distintas zonas del condado.

2. Los exámenes realizados a plazos de 2 a 4 años revelaron que 27 niños blancos y 4 de color habían adquirido calcificación pulmonar; todos ellos eran menores de 15 años. Este hallazgo, y la elevada frecuencia a la edad de 7 a 9

años, indica que los niños del Condado de Williamson adquieren la calcificación pulmonar a una edad muy temprana. Muchos de los niños con calcificación no revelaron sensibilidad a la tuberculina.

3. Al estudiar la calcificación pulmonar en relación con la sensibilidad a la tuberculina, descubrióse que la última, calculada sobre una base de 0.01 mg. de TA, resultó más frecuente entre los niños con calcificación que entre los demás.

Acknowledgment is made of the valuable suggestions of Dr. J. A. Doull in the preparation of this report.

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INTRAPLEURAL AND EXTRAPLEURAL OLEOTHORAX[1]

A Report on Its Use in Thirty-six Negro Patients

REUBEN HOFFMAN AND MARTIN KETTLER

INDICATIONS

The chief indications for the intrapleural use of oil as reported in a comprehensive compilation by Joannides (1) and Howlett (2) are the prevention of progressive obliteration, occurring in the course of pneumothorax therapy; in chronic pleurisies with effusions; and in tuberculous empyema. Some of the limited indications are to improve a pneumothorax collapse and as a substitute for pneumothorax when post-sanatorium refills are impossible to obtain; latterly, in extrapleural pneumonolysis to combat infection or obliteration of the extrapleural space (3) and routinely as a means of compression to maintain an extrapleural space (4).

Our indications are in essential agreement with the above. However, we object to the use of oleothorax as a method of improving a collapse achieved by pneumothorax; we use it only as a substitute measure for an effective pneumothorax under certain conditions. In addition, we employ oleothorax as a routine procedure to maintain the extrapleural space created by the extrapleural pneumonolysis. These and a few minor modifications are referred to in the following paragraphs dealing with indications.

Obliterative pleuritis: We have encountered obliterative pleuritis, resulting in loss of pneumothorax space, in 6.2 per cent of 149 effective pneumothoraces. In the cases where the reëxpansion occurred early in the course of the therapy, it was almost invariably followed by progression of the disease. When the reexpansion occurred late (two or more years), it was still followed by a significant number of activations. The progression or activation of the disease presented the problem of utilizing a more radical collapse measure or the abandonment, temporary or permanent, of all collapse procedures. Since the original plan on instituting the pneumothorax was to maintain the collapse for a time sufficient to bring about healing, it became necessary to use the one substitute measure, oleothorax, which would most successfully maintain the collapse.

Recurrent effusions: Large, recurrent effusions, occurring during the course of pneumothorax therapy, were found to be a definite indication for replacement with oil. The fluid, even if initially negative for tubercle bacilli, is usually the forerunner of infection leading to frank tuberculous empyema. The importance of combating these rapidly recurring effusions, which necessitate frequent aspirations, lies in the fact that they constitute a definite threat to the safe continuation of the pneumothorax therapy, either forcing abandonment of the pneumothorax or resulting in obliteration.

Tuberculous empyema: The treatment of tuberculous empyema, complicating artificial pneumothorax, depends upon the status of the lesion in the underlying

[1] From the Maryland Tuberculosis Sanatorium (Colored Branch), Henryton, Maryland.

lung. When the pulmonary lesion cannot be controlled, a thoracoplasty will be the only effective method. In those cases of empyema where the pulmonary lesion is controlled, conservative treatment with frequent aspirations and irrigations with antiseptics is known to be an ineffective method, even though the condition of the patient may improve for a time. As long as there remains a free pleural space, the empyema will recur. When a sufficient trial with aspirations and irrigations with antiseptics has failed, oleothorax should be employed for, if successful, a thoracoplasty can be postponed or avoided entirely.

Substitution for pneumothorax: Our patients from rural Maryland are, with few isolated exceptions, unable to continue their pneumothorax refills after discharge from the sanatorium due to lack of facilities and transportation difficulties. Further, a significant number of our patients were found to be too inconstant in their attendance (or failed to attend at all) even where facilities were adequate. The consequence is an early loss of an effective pneumothorax. We have met these problems by employing oleothorax as a substitute for pneumothorax.

Extrapleural pneumothorax: Maintenance of an extrapleural space by air refills, following an extrapleural pneumonolysis, has been found difficult. The difficulties encountered were either premature obliteration or infection, leading to ultimate loss of the space. To obviate obliteration, minimize infection and insure a permanent collapse, we routinely employ oleothorax as a replacement measure in extrapleural pneumothorax.

Regardless of the indication for which the oil is employed, its success depends upon rigid adherence to the following conditions: absence of adhesions in intrapleural pneumothorax; an effective, well established pneumothorax; negative sputum; and, in the case of empyema, the patient must have reached a relatively afebrile state. These conditions will limit the number of available cases amenable to oleothorax, but at the same time will lessen the number of complications and unsatisfactory end-results.

TECHNIQUE

Intrapleural pneumothorax: We found the schedule of oil injections for intrapleural oleothorax as described by Howlett (2) very satisfactory. Each patient demands a slight individual variation. Commercial olive oil with gomenol, 3 to 5 per cent by volume, was employed in all our cases. Routine asepsis of pneumothorax technique was observed. A suitable length of rubber tubing was placed between the needle and syringe to prevent displacement of the needle on manipulation of the syringe. The site of insertion of the needle was changed at each injection to minimize trauma to the pleura. At the completion of each injection the pressure in the pleural cavity was adjusted to zero. It is important to compare the initial intrapleural pressure at each subsequent injection with the terminal pressure of the preceding injection. A sharp rise in the initial pressure at a subsequent refill, with the patient in the *same position*, was found to indicate the formation of an effusion. No attempt was made to completely fill the pleural cavity with oil. At the last instillation approximately 100 cc. of air was left in the pleural cavity, which was absorbed in about four weeks.

The average time necessary to fill the pleural cavity with oil was thirty days.

Extrapleural pneumothorax: Providing a proper selection of the type of lesion was made, the success of maintaining the extrapleural pneumothorax depends upon the postoperative management. If that is carried out properly, infection will be seldom encountered and the extrapleural space will be easily maintained until it is safe to be replaced by oil. We continue air refills for eight to ten weeks after the operation. In this period of time all postoperative reactions will have subsided and the collapse can be stabilized with weekly (or longer) air refills.

The replacement of an extrapleural pneumothorax with oil then follows the same principles as those for intrapleural oleothorax, with the difference that the ensuing air pressures will be high. The first anterior interspace is used as the site of injection. If the needle be inserted too low there is danger of penetrating the lung, since the collapse may be saucer-shaped with the periphery of the lung at a higher level than the central portion. The average time to complete an extrapleural pneumothorax was fourteen days.

MATERIAL AND RESULTS

Oleothorax was employed intrapleurally and extrapleurally in 36 patients. The following tabulation records the indications and number of cases in the two groups.

Indications	Intrapleural	Extrapleural
Obliterative pleuritis	14	—
Recurrent effusions	7	—
Substitute for pneumothorax	6	—
Empyema	2	—
Routine replacement of extrapleural pneumothorax	—	7
	—	—
	29	7

Bilateral collapse therapy was successfully carried out in 5 cases of the intrapleural group; in 2 in whom a contralateral phrenic nerve crush was performed subsequently and in 3 in whom a contralateral pneumothorax was being maintained. In the extrapleural group there were 4 cases with bilateral collapse. In the first case a first-stage thoracoplasty on the left side was followed by activation of a lesion in the upper lobe on the right side. The second stage was postponed and the right side controlled by an extrapleural pneumonolysis and extrapleural pneumothorax with subsequent replacement with oil. The thoracoplasty on the left side was then successfully completed by an additional two-stage operation. In the second case a first-stage thoracoplasty on the left side was followed

FIGS. 1–6

FIG. 1 (upper left). Case 1. Shows a one-stage thoracoplasty on the left. An extrapleural pneumonolysis on the right performed to control a postoperative spread.

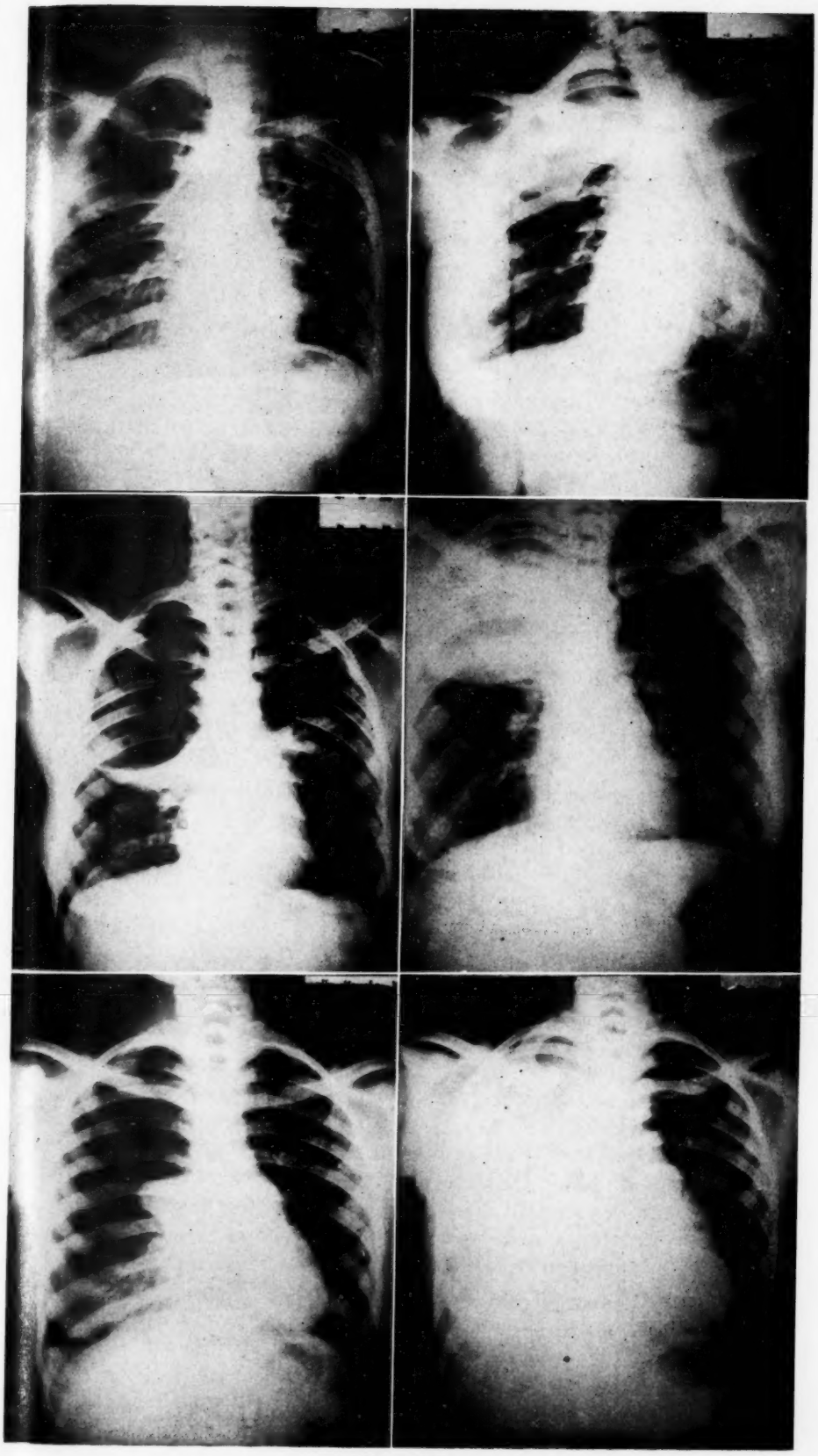
FIG. 2 (upper right). Case 1. The extrapleural pneumothorax was replaced by oil. The thoracoplasty on the left was completed by two additional stages.

FIG. 3 (center left). Case 2. Shows an extrapleural pneumothorax on the right.

FIG. 4 (center right). Case 2. Shows the extrapleural pneumothorax replaced with oil.

FIG. 5 (lower left). Case 3. Shows an effective pneumothorax after closed pneumonolysis.

FIG. 6 (lower right). Case 3. No facilities for post-sanatorium refills; pneumothorax substituted by oleothorax.



FIGS. 1–6

by the appearance of a fresh lesion in the upper lobe on the right side. This case was managed in the same manner as the first case with a successful result. The third and fourth cases had an effective intrapleural pneumothorax on one side prior to an extrapleural pneumonolysis on the other side.

The longest period of observation in the intrapleural group is thirty-three months, the shortest four months, the average fourteen months; in the extrapleural group twenty-one months, six months, fifteen months.

Thirty patients were discharged and have resumed work. Three patients are still in the sanatorium and ready for discharge. One patient developed an empyema and the oil was withdrawn. One patient developed a severe contralateral lesion, the oil was withdrawn and the pneumothorax reëstablished. One is doing poorly because of a contralateral lesion, although the oleothorax has been carried successfully for thirty-three months.

COMPLICATIONS

Bronchopleural fistula with resulting empyema was not encountered in this series. In the cases reported in the literature no proof is offered that there is a causal relationship between the occurrence of the bronchopleural fistula and the presence of the oleothorax. Proof is necessary since spontaneous erosions occur in uncollapsed lungs, in the presence of artificial pneumothorax and in the presence of a tuberculous empyema. A higher incidence of bronchopleural fistula can be expected when oil is used in order to achieve a better collapse in the presence of adhesions. For, under these circumstances, the incidence of bronchopleural fistula (due to rupture of the lung near the attachment of adhesions) will be increased by the additional hazard of the slightly positive pressure employed and by the weight of the oil.

Empyema was encountered in 3 cases: 2 in the extrapleural group and one in the intrapleural group. In both cases of the extrapleural group the infection was treated by aspiration, irrigation with antiseptics and successful reëstablishment of the oleothorax. In the one case of the intrapleural group a large purulent effusion developed four months after completion of the oleothorax. The effusion was negative for tubercle bacilli. The oil was withdrawn and, at the present writing, the effusion is responding well to irrigation with antiseptics.

Significantly, in none of these cases did the complications interfere with the maintenance of the collapse.

Large effusions complicating the oleothorax were not encountered. Small sterile effusions were seen in half of the cases, but did not interfere with the management of the oleothorax and were disregarded.

Oil seepage and needle tract infection were not encountered. We feel that this complication was averted by the expulsion of the few drops of oil from the needle before withdrawal, careful massage of the site of injection and by the patient lying on the untreated side for six hours after each injection.

Following the completion of the oleothorax no additional refills were given because no absorption of oil could be demonstrated in any of our cases.

COMMENT

The objection to the use of oil to maintain an extrapleural collapse after an extrapleural pneumonolysis, as gathered from a review of the recent literature, is based on the assumption that complications are inevitable and on the dictum that the procedure will be irreversible due to permanent contraction of the compressed lung. We have encountered no late complications as yet. The spectre of irreversibility has not arisen, since we have not had cause to abandon the oleothorax in any patient in the extrapleural group. In 4 patients with an effective collapse of one side, a successful end-result was obtained only because we were able to control the other side with extrapleural pneumonolysis followed by replacement with oil. Prior to our practice of routine replacement of the extrapleural pneumothorax with oleothorax, in each one of 5 cases subjected to an extrapleural pneumonolysis, in which the maintenance of the space was attempted by air refills, ultimate infection or obliteration of the space occurred. By contrast, in the 7 consecutive cases of extrapleural oleothorax, included in this paper, no untoward effects were encountered and no reëxpansion of the lung occurred.

CONCLUSIONS

We found oleothorax, employed as a substitute measure for intrapleural and extrapleural pneumothorax, a desirable adjunct to other forms of collapse therapy of pulmonary tuberculosis. It is highly useful in cases in which the indications are properly chosen and in which rigid adherence to indications is observed.

CONCLUSIONES

Empleado como substituto del neumotórax intra y extrapleural, el oleotórax resultó ser un coadyuvante conveniente de otras formas de la colapsoterapia de la tuberculosis pulmonar. Resulta utilísimo en los casos en que se escogen debidamente las indicaciones y en que se observan rígidamente éstas.

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TUBERCULOUS EMPYEMA COMPLICATING INDUCED PNEUMOTHORAX[1,2]

JOSEPH GOORWITCH[3]

DEFINITION

In the American literature of the last two decades ten different definitions are encountered. Standard textbooks still define tuberculous empyema as a collection of tuberculous pus in the pleural cavity or as suppurative pleurisy resulting from infection with the tubercle bacillus (3, 8, 61).

This conception prevailed until about 1930 when Archibald of Montreal, in laying down broader indications for major surgical intervention, included in the term of pure tuberculous empyema all turbid and nonpurulent pleural fluids which bacteriologically and clinically resembled purulent fluids (2). In 1937 Woodruff liberalized the diagnostic criteria of pure tuberculous empyema further by including turbid fluids in the presence of pulmonary tuberculosis and any fluid containing tubercle bacilli on direct smear (80, 50, 69); this, of course, includes the great majority of all effusions complicating pneumothorax in tuberculous subjects.

The strict conception of tuberculous empyema is represented in recent literature by DeCecio and Potter whose diagnostic criteria include not only the presence of frank pus containing tubercle bacilli but also a clinical picture of rapid formation of exudate accompanied by prolonged fever and constitutional decline as the chronicity of empyema is established (19).

There are two strong objections to the liberal application of the term pure tuberculous empyema; inasmuch as the word empyema means a collection of pus, it is obviously both illogical and unscientific to speak of "nonpurulent empyema." The second objection is the fact that prognosis and treatment of serous effusions are not similar to those of purulent effusions and, therefore, unless the term is accurately defined, comparison of results of treatment by different methods will have but little meaning.

Jones and Alexander's definition seems to be the most satisfactory: a collection of purulent pleural fluid containing tubercle bacilli or accompanied by pulmonary tuberculosis or histological evidence of tuberculous pleuritis (40). In this paper, by purulent fluid is meant an opaque fluid of varying consistency which is to be distinguished from serous fluid described as clear, cloudy, turbid, translucent or opalescent.

PATHOGENESIS

Exudative pleuritis accompanying pulmonary tuberculosis of the same type is mentioned in the literature (10, 12, 45, 70, 76), but the most convincing ex-

[1] From Olive View Sanatorium, Olive View, California.

[2] Read at the Clinical-Pathological Conference of the Olive View Sanatorium in August, 1942.

[3] 852 Hagar Street, San Fernando, California.

planation of the pathogenesis of tuberculous empyema encountered is ulceration of a caseating subpleural focus into a patent pleural space (15, 35, 43, 45, 53, 56, 51, 69, 79). This conception apparently assumes the existence of a pleural-pulmonary communication without actual communication between the pleural space and a bronchus, at least in those cases in which clinical evidence of a patent bronchopleural fistula is absent. In 1937, Coryllos introduced the concept of tuberculous empyema as due to bronchopleural fistula, even in the absence of all usual manifestations of fistula. The absence of these signs in the majority of pure tuberculous empyemata he explained by the high incidence of punctiform fistulae which seal over very rapidly; recurrence of empyema he ascribed to reopening of the fistula (15). In the latest reports from Sea View Hospital, 39 per cent of 67 tuberculous empyemata "occurred within one month if the thoracoscopy with or without severance of adhesions," and showed incontrovertible evidence of bronchopleural fistula (52, 55). It is not clear why thoracoscopy alone should figure so prominently in the incidence of bronchopleural fistula and empyema.

In the absence of pneumothorax, tuberculous empyema is not common because of the strong tendency of superficial lesions to form adhesions between the visceral and parietal pleurae and thus become localized (12, 15, 20, 22, 45, 50, 52, 56, 59, 76). This universal interpretation is supported by the disproportionately greater incidence of effusions in mechanically unsatisfactory as compared to mechanically satisfactory pneumothorax; in other words, the rôle of superficial lesions in the pathogenesis of pleural effusions is unmistakable due to their association with pleural adhesions. Although the absence of a pleural effusion does not exclude the existence of superficial lesions, its presence justifies the assumption that subpleural tuberculous foci involving the pleura are probably present too.

In tuberculous subjects the almost universal presence of tubercle bacilli in purulent fluids has been reported consistently (10, 24, 29, 40, 42, 49, 52, 57, 76, 82) and their high incidence in serous fluids very frequently (10, 19, 24, 29, 56, 58, 82). These findings plus the characteristics of exudates claimed for these serous effusions constitute sufficient evidence for the belief that, with the exception of minimal fleeting and asymptomatic effusions, probably all effusions complicating induced pneumothorax in the tuberculous are themselves tuberculous (10, 12, 56, 58).

Whether the effusion is purulent at onset, or becomes so later, and its clinical manifestations probably depend to a high degree on the quantity of caseous tissue and tubercle bacilli spilled from superficial ulcerative pulmonary lesions into the pleural space (15, 46). Experimental studies of tuberculous empyema warranted the conclusion that (bovine) tubercle bacilli alone in the pneumothorax space of sensitized rabbits having a subpleural focus do not produce a purulent effusion unless the superficial tuberculous focus ulcerates and its caseous content is spilled into the pleural cavity; this conclusion is based on the presence of microscopical evidence of ulceration of subpleural lesions in every case of empyema and its absence in the cases of serous effusions (53).

Inasmuch as there is no positive clinical or other evidence to support the

various other factors mentioned in the literature as responsible for the formation of tuberculous effusions, except the asymptomatic fleeting minimal effusions, their discussion in this study is omitted (4, 10, 12, 15, 43, 45, 48, 51, 58, 56, 74 78, 82). Obviously, injudicious pneumothorax refills, with or without "positive" intrapleural pressures, resulting in empyema by virtue of rupture of a pulmonary lesion through a pleural adhesion, are not a distinct aetiological factor, but merely represent the extreme degree of trauma to a susceptible lesion (43, 68, 73). The same reasoning applies to the rôle of closed intrapleural pneumonolysis in the production of empyema (15, 16, 43, 51, 52, 56, 68). In the Olive View Sanatorium experience from July, 1940 to July, 1942, only about one-fourth of the 133 closed pneumonolyses done were complicated by pleural effusions of any kind within the first postoperative month. Most of these effusions were small, serous and asymptomatic; all were aspirated and over one-half of them were found to contain tubercle bacilli demonstrable on culture. This incidence of effusions with tubercle bacilli suggests that, in closed pneumonolysis, pleural effusions, other than the minimal, fleeting and asymptomatic, are not a mere response to irritation by the heat of the cautery but a result of trauma to a tuberculous lesion, pulmonary or pleural.

TREATMENT

Some of the accompaniments and complications of pure tuberculous empyema which treatment is designed to prevent or minimize are the following: toxaemia, secondary anaemia, amyloidosis, *empyema necessitatis*, premature reëxpansion of the lung, delayed reëxpansion, unexpandability due to thickening and fibrosis of the visceral pleura or to heavy paravertebral adhesions and fixation of the mediastinum and the hemidiaphragm and, finally, the development of reopening of a bronchopleural fistula which, if large enough, will lead to conversion into mixed tuberculous empyema with frequent bilateralization of disease and fatal ending.

The problem of treatment is still controversial. Attempts to demonstrate that pure tuberculous empyema, at least in the presence of controlled pulmonary disease, is a medical problem and that adequate conservative treatment could reduce considerably the number of cases requiring major surgical intervention have not been successful until recently. A great variety of substances had at one time or another been reported to be effective in the intrapleural medication of tuberculous empyema. In recent years successful results (obliteration of pleural space and, where pneumothorax is maintained, complete disappearance of all pus or persistence of only very small amounts of serous fluids) were claimed in 50 per cent or more of cases with the use of the following: saline (48), merthiolate (10), azochloramide (24), gomenol in cotton-seed oil (9), or paraffine oil (43) and Azo-T (azochloramide 1:2,000 and triethanolamine 1:800) (52, 55).

The use of neoprontosil, a sulfonamide, formerly known as prontosil, in tuberculous empyema was first mentioned by Schlenker in 1938 (66). He reported 2 patients with sterile purulent effusions complicating induced pneumothorax. Five to 10 cc. of prontosil were instilled intrapleurally after complete aspiration of fluid every three to seven days. In addition, 5 cc. of prontosil were injected

intramuscularly every one to three days. The pleural route was thought to be the more effective. The pleural space was not irrigated. Soon after the institution of treatment there was general improvement and the fever slowly declined; the fluid became less purulent and reformed more slowly until it disappeared entirely in an average of ninety-two days from onset and fifty-three days from the time the use of prontosil was begun. The average total volume of fluid aspirated was 4,600 cc. in an average of 15 sittings during an average period of forty-eight days. The only residual changes following conclusion of treatment of empyema were a rise in intrapleural pressures and considerable reëxpansion of the lung, although pulmonary disease remained controlled. Four months following disappearance of fluid, both patients were in good clinical condition and enjoying ambulatory privileges. In 1939 2 more patients were described by the same author as successfully treated by the use of prontosil (67).

In 1940 a South American publication carried a report of 4 pure tuberculous empyemata cured by intrapleural injections of 5 cc. prontosil (5 per cent) every three to four days after complete aspirations. Fever disappeared in two to fourteen days and the pus thinned out in two to four days after the first treatment. The patients were stated to have remained cured for two to eighteen months and an average of eight months (5).

At Olive View Sanatorium between August, 1939 and September, 1940, I had the opportunity to employ neoprontosil in the treatment of 12 consecutive, unselected cases of empyema with tubercle bacilli and no other organisms. In all cases the purulent fluid was preceded by a febrile serous effusion complicating induced unilateral pneumothorax of an average duration of eight months; there was nothing in their history suggestive of bronchopleural fistula. Prior to arrival on my wards all 12 were treated by aspiration, irrigation and/or instillation of antiseptics and dyes for an average of eight months.

Status of Patients Treated with Neoprontosil

Sex	Male	6	Race	White	4
	Female	6		Mexican	5
				Negro	3
Age	Range	16–48	Side	Right	8
	Average	34		Left	4

Status of Patients just prior to the Institution of Treatment with Neoprontosil

Extent	Moderately advanced	3	Cavitation	Collapsed lung	4
	Far advanced	9		Uncollapsed lung (or contralateral)	2
Distribution	Unilateral	8	Sputum	Positive	6
	Bilateral	4		Negative	6
Predominant type	Exudative	8	Fever	Moderately febrile	5
	Fibrotic	4		Afebrile	7
Type of pneumothorax			Mechanically satisfactory		3
			Mechanically unsatisfactory		9

Character of pus	Thin	7
	Very thick	5
Interval between induction of pneumothorax and onset of effusion (months)	Range	1–22
	Average	8
Interval between induction of pneumothorax and institution of neoprontosil therapy (months)	Range	6–23
	Average	16

Upon arrival of these patients on my wards complete aspirations of the purulent fluid were carried out and, without irrigating the pleural cavity, 2.5 per cent neoprontosil solution was instilled. This was repeated at semiweekly to biweekly intervals depending on the rate of reformation of the fluid and its character; the volume of neoprontosil instilled at a sitting varied from 5 cc., when medication was begun, to 40 cc. later on, the amount generally in proportion to the volume of pus present and the size of the empyema cavity. Following treatment the patients were instructed to stay off the empyema side for the balance of the day but to change sides freely afterwards to get all of the interior of the empyema cavity in contact with the solution.

Depending on whether maintenance of collapse was desired or not, air refills were given or air was aspirated at the conclusion of each treatment; the latter was continued until markedly "negative" intrapleural pressures were reached or the patient complained of chest discomfort. No medication of the needle tract was practiced in the 465 pleural punctures done; the final step in each treatment was the instillation of neoprontosil. Aspirations were continued as long as any amount of any type of fluid remained; instillations of neoprontosil, however, were discontinued as soon as the fluid became serous.

Treatment

(August, 1939 to August, 1940)

Pneumothorax	Maintained	2
	Reëxpansion attempted	10
Homolateral phrenemphraxis		3
Duration of treatment per patient (months)	Range	3–11
	Average	6
Number of aspirations per patient	Range	15–67
	Average	39
Total volume of fluid aspirated per patient	Range	700–5,400 cc.
	Average	2,000 cc.
Average volume of fluid aspirated per patient, per sitting		50 cc.

Initial results of treatment were very similar to those described by Schlenker, using prontosil (66, 67) and by the Sea View workers using Azo-T (52, 55). However, after the first month results were not as good as those described by Schlenker; it is possible that omission of intramuscular medication and the

longer duration of empyema in this series (average of eight months compared to forty days in Schlenker's patients) were partially responsible for the slower response here (30).

The only complication of treatment encountered was a single instance of chest wall abscess along the anterioraxillary line in a patient with a very small amount of intrapleural pus that was on the point of disappearance. Frequent aspirations of pus from the small abscess which communicated with the pleural cavity and replacement with neoprontosil resulted in complete healing without a break in the overlying skin. No mixed infection developed in any of the patients, which compares favorably with published reports (2, 6, 51, 76, 80).

Results of Treatment

		Early (August, 1940)	*Late (August, 1942)*
Fluid	Entirely absent	7	10
	Lung still collapsed	3	4
	Lung reëxpanded	4	6
	Serous and persists in small amounts	5	2(thin pus)
	Lung still collapsed	5	2
	Lung reëxpanded	0	0
Pneumothorax	Present	8	2
	Intentionally maintained	2	1
	Despite attempt to reëxpand	6	1
	Mechanically satisfactory	2	0
	Mechanically unsatisfactory	6	2
	Fluid absent	3	1
	Fluid present	5	1
	Absent	4	10
	Discontinued	4	9
	Lost	0	1
	Fluid absent	4	10
	Fluid present	0	0
Number of months since final aspiration at Olive View	For entire series: Range	0–8	0–27
	For entire series: Average	2	15
	For those free of fluid (7): Range	1–8	3–27
	For those free of fluid (7): Average	3½	19

In September, 1940, due to an abrupt change of services, both neoprontosil and metaphen in peanut oil were irregularly used for persisting effusions with disappointing results. During 1941, 4 patients were subjected to thoracoplasty, 3 homolateral and one contralateral; in all cases the indication was patent pulmonary cavitation with positive sputum and not empyema, and in only one case was it necessary to do an additional thoracoplasty stage for the obliteration of a residual empyema pocket. Contralateral pneumothorax was induced for cavitation in 2 patients but was abandoned as ineffective.

Table 4 presents the results of treatment, early (30) and late, of these 12 patients. The 2 patients in whom fluid persists to date left Olive View Sana-

torium without approval late in 1940 and never reëntered. One of them has an unexpandable lung and thoracoplasty is being considered for her; the other patient developed a chest wall abscess while under treatment by aspiration and methylene blue instillation in an outside clinic and was hospitalized; the empyema was drained by rib resection and at present the patient is too ill for thoracoplasty. Two other patients died early in 1942, one from progressing pulmonary tuberculosis and the other from extensive intestinal tuberclosis.

Of the 10 living patients, 2 are unimproved, 3 are improved, one is apparently arrested and 4 are arrested. The 5 patients in the last two groups mentioned are at home working or doing their housework.

CONCLUSIONS

Major surgical collapse yields and will continue to yield a higher percentage of permanently successful results than aspiration and intrapleural medication with no matter how efficacious a preparation. This situation is due to the underlying pathological factors, to the fact that the great majority of pneumothoraces complicated by tuberculous empyema is both ineffective because of persistence of patent pulmonary cavitation and mechanically unsatisfactory by virtue of the presence of adhesions. Such cases, therefore, yield best results when major surgical collapse is employed to obliterate both pulmonary and pleural cavities.

If nonsurgical treatment of pure tuberculous empyema could be completely freed, as it seems to be the case, from such complications as chest wall infections, it would be of definite value even in cases where thoracoplasty is indicated for patient pulmonary cavitation. In such cases careful conservative medication, begun immediately at the onset of empyema and continued for an arbitrarily brief period not exceeding two months, can be counted on to prevent the complications listed elsewhere in this paper and to insure better surgical results by improving the patient's general condition and by causing the disappearance of purulent fluid or its conversion into a small serous one (10).

According to Burrell, Alexander and Coryllos good results in treatment by aspiration, irrigation and instillation of bactericidal agents could not be ascribed to chemical action but were due to simple mechanical cleansing action (12, 15) or healing of pleural-pulmonary communications (15). Whatever the mechanism, results can be improved by instituting frequent (13) and complete aspirations and instillations of sufficient volumes of medicated solution (52) to make contact certain with all parts of the pleural cavity, in different body postures. In the case of neoprontosil and Azo-T, with irrigations omitted, cleansing action, pure and simple, could hardly account for the satisfactory results reported.

The above should not be taken as a recommendation for a universal method of attack on tuberculous empyema. In the end the best treatment is the individualized treatment. In deciding upon the most promising type of therapy in a given case of pure tuberculous empyema complicating induced pneumothorax, the following question must be answered: Is the pulmonary process controlled by the pneumothorax? If the answer is in the affirmative, the question arises as to whether the type and extent of pulmonary disease is such as to warrant an

eventual reëxpansion, or whether permanent arrest can be achieved by irreversible collapse only.

When temporary collapse is thought to be sufficient, conservative therapy of the empyema as outlined and maintenance of pneumothorax are indicated until such a time as reëxpansion is considered safe; this course of treatment should be given careful consideration as it may result in an unexpandable lung and/or bronchopleural fistula, the incidence of this complication varying considerably according to reports in the literature. If irreversible surgical collapse is thought necessary for permanent arrest, the course of treatment should be the same as if pulmonary disease remained uncontrolled in spite of treatment by pneumothorax, that is, air refills must be discontinued, the empyema treated as outlined and preparations made for thoracoplasty, provided that major surgical intervention is not contraindicated.

As always, prevention is to be preferred to cure. Prevention of empyema is based on and is inseparable from the prevention of serous effusions and this, in turn, depends on early discontinuation of pneumothoraces which do not control the pulmonary process for which they were induced. Thus the incidence of tuberculous empyema in the course of induced pneumothorax could be reduced to a minimum by remembering, first, that purulent fluids are preceded in the majority of cases by serous effusions (8, 22, 24, 33, 48, 51, 56, 82) and, second, that the great majority of effusions both serous and purulent arise early in the course of mechanically unsatisfactory pneumothoraces (10, 12, 15, 17, 22, 45, 51, 73, 78, 80, 82).

The unavoidably logical corrolaries are in the form of "not's":

(*1*) Not to continue pneumothoraces which are not satisfactory (10, 17, 51) and cannot be rendered satisfactory by means of intrapleural pneumonolysis (16, 19, 68, 69, 73, 76, 82) beyond an arbitrarily brief period, such as a maximum of three months.

(*2*) Not to "push" pneumothoraces for the purpose of stretching or breaking adhesions (15, 43, 52, 56, 68, 76, 78) and not to give large refills at long intervals in order to avoid wide fluctuations in intrapleural pressures (45, 68, 78).

(*3*) Not to allow serous effusions to accumulate because they appear to be innocuous, but to maintain as dry a pneumothorax space as possible (13, 22, 24, 26, 43, 46, 48, 49, 68, 80, 82) and in the presence of ineffective collapse to aspirate the fluid, discontinue air refills and substitute an effective collapse procedure.

An additional argument for the prevention of pleural effusions, and especially empyema, is the relatively recent bronchospirometric data which indicate that pleural involvement is the greatest single contributor to impaired pulmonary function.

SUMMARY

1. A review of some of the literature of the last two decades and personal impressions and experiences with tuberculous empyema complicating induced pneumothorax are presented.

2. The term tuberculous empyema is discussed and for the sake of greater

uniformity it is recommended that serous effusions be excluded and the term reserved for purulent effusions either containing tubercle bacilli or associated with pulmonary or pleural tuberculosis.

3. In the pathogenesis of tuberculous empyema the only factors considered to be of aetiological significance, and therefore discussed, are: bronchopleural fistula, tiny and superficial pleuropulmonary communication and exudative tuberculous lesions of the pleura. The universal demonstrability of tubercle bacilli in purulent effusions and experimental, autoptic and histological studies afford ample support. The greater incidence of effusions in mechanically unsatisfactory pneumothoraces, as compared to satisfactory ones, is taken to mean that in tuberculosis adhesions are very probably synonymous with the presence of pleuropulmonary lesions.

4. The aims of treatment of tuberculous empyema are listed and the value of vigorous aspiration and intrapleural medication, at least temporarily, even in those cases eventually to be subjected to thoracoplasty, is pointed out. Favorable results and an almost complete absence of complications with the use of neoprontosil in pure tuberculous empyema are reported in an admittedly small series. Some points in technique are described and the value of attention to detail is stressed. Significant factors in determining the type of treatment indicated are discussed in the realization that the best treatment must be individualized.

5. The intimate relation among mechanically ineffective pneumothorax, serous effusions and empyema is pointed out and suggestions as to how to avoid empyema as a complication of induced pneumothorax are made. Prevention of tuberculous empyema is easier and more effective than treatment.

SUMARIO

1. En este trabajo preséntase un repaso de parte de la literatura de los dos últimos decenios y las impresiones y observaciones personales del autor con respecto al empiema tuberculoso como complicación del neumotórax artificial.

2. Discútese el término de empiema tuberculoso y en aras de la uniformidad recomiéndase que se excluyan del mismo los derrames serosos, reservándolo para los derrames purulentos que o bien contienen bacilos tuberculosos o están asociados con tuberculosis pulmonar o pleural.

3. En la patogenia del empiema tuberculoso los únicos factores considerados de importancia etiológica y que por lo tanto se discuten, son: la fístula broncopleural, la comunicación pleuropulmonar superficial y las lesiones tuberculosas exudativas de la pleura. La demostrabilidad universal de los bacilos tuberculosos en los derrames purulentos, y los estudios experimentales, autópsicos e histológicos, ofrecen amplio apoyo. La mayor frecuencia de los derrames en el neumotórax mecánicamente deficiente, comparado con el neumotórax satisfactorio, se interpreta en el sentido de que en la tuberculosis las adherencias, con toda probabilidad, representan lesiones pleuropulmonares.

4. Comunícanse los propósitos del tratamiento del empiema tuberculoso y señálase el valor de la aspiración enérgica y de la medicación intrapleural, por

lo menos temporalmente, aun en los casos que más tarde tendrán que ser sometidos a la toracoplastia. En una serie reconocidamente pequeña, comunícanse los resultados favorables obtenidos con el neoprontosil en el empiema tuberculoso puro, sin que apenas sobrevinieran complicaciones. Descríbense algunos puntos de la técnica y se recalca la importancia de prestar atención a los detalles. Por comprenderse que hay que individualizar el tratamiento, discútense los factores significativos para determinar la terapéutica indicada.

5. Puntualízase la relación íntima que existe entre un neumotórax mecénicamente ineficaz, los derrames serosos y el empiema, y ofrécense indicaciones en cuanto a la manera de evitar el empiema como complicación del neumotórax provocado. La profilaxis del empiema tuberculoso es más fácil y más eficaz que el tratamiento.

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GOLD THERAPY IN TUBERCULOSIS[1,2]

ARTHUR REST

The enthusiasm of the phthisiologist was greatly aroused when Møllgaard and his collaborators (1) published their book in 1924, on *The Chemotherapy of Tuberculosis*. They were positive in their contention that their preparation sanocrysin (gold sodium thiosulphate) would cure pulmonary tuberculosis. Henrichsen and Sweany (2) published a supplement on *Sanocrysin Treatment in Tuberculosis* to the October, 1933, number of the AMERICAN REVIEW OF TUBERCULOSIS. They studied 5 moderately advanced and 61 far advanced adult male tuberculous patients treated with sanocrysin. These authors concluded that "(*a*) about 50 per cent of tuberculous patients having a stationary or downward progressive advanced tuberculosis of the 'B' or 'C' types when given sanocrysin in well-regulated doses, will show a rather prompt cessation of symptoms (drop of temperature and pulse, increase of weight and improvement of the general condition), which changes tend to be permanent if the patient observes the usual measures of hygiene; (*b*) a clearing of tuberculous infiltration, with marked fibrosis and contraction of cavities, as shown by X-rays; and (*c*) changes from unfavorable to favorable laboratory findings. The remainder of the treated patients may be divided about equally into three classes: Those who show a temporary improvement for a few weeks to a few months, those who show no favorable change, and those who will not tolerate the drug at all."

These conclusions so impressed the late Dr. Herman Schwatt, formerly medical director of the Sanatorium of the Jewish Consumptives' Relief Society, that he introduced gold therapy in this institution in June, 1934. At the October, 1934 meeting of the Denver Sanatorium Association he presented a preliminary report on the use of gold in tuberculosis. His study embraced a series of 30 cases. He concluded that, (*1*) gold sodium thiosulphate is not a specific, (*2*) our experience so far encourages us to believe that in this drug we have a valuable phthisiotherapeutic remedy in carefully selected cases, (*3*) it can be administered without any great fear of serious complications, (*4*) even a small percentage of favorable effects justify the treatment in view of the fact that in most cases no other effective method of treatment is available. In his premature report no complications whatsoever were met with except albuminuria and the occurrence of renal epithelial cells and occasionally small casts in the urine. One year later, a paper on *The Value of the Patch Test in Gold Therapy* was presented by me (3) before the Denver Sanatorium Association. The picture changed.

[1] From the Medical Department of the Sanatorium of the Jewish Consumptives' Relief Society, Spivak, Colorado.

[2] Presented before a meeting of the Denver Sanatorium Association at Spivak, Colorado, October 28, 1941.

In 42 cases, the following complications were met with:

(a) 4 had stomatitis
(b) 3 had papular dermatitis
(c) 1 developed an exfoliative dermatitic
(d) 1 developed a haemolytic jaundice
(e) 3 had gastro-intestinal symptoms
All showed albumin and pus cells—some presented hyaline and granular casts.

The therapy was discontinued in 1938. One patient recently received gold for *tuberculosis cutis orificialis*. Ample opportunity has been afforded me to analyze my series of 110 cases and to substantiate or disprove the conclusions of the late Doctor Schwatt. The views of Møllgaard stimulated an enormous amount of experimental and clinical work with gold. The literature has reached great proportions and is so controversial that one's own experience with the drug should decide its merits rather than the confusing opinion of others.

At first we used sanocrysin which was imported from Denmark. This is a crystalline substance, easily soluble in the proportion of 1 g. of sanocrysin to 2 g. of sterile water and is given intravenously. Subsequently, gold sodium thiosulphate made by Abbott and chemically the same as sanocrysin was used. Later the Danish preparation, oleosanocrysin, which is a suspension of gold sodium thiosulphate in an oily medium, was substituted. This is given intramuscularly and is injected in the buttocks. The advantages of this preparation were explained in that there was no need to search for a vein, there was less danger from shock as might occur in intravenous injection, absorption of the gold was slower and complications less frequent.

The selected patients had daily urinalyses for a week for albumin and abnormal microscopical constituents. Phenolsulphonphthalein test, urine concentration and dilution tests were performed. Only those patients who showed no evidence of kidney damage were chosen. In addition the following examinations were made: nonprotein nitrogen and uric acid determinations; Schilling blood count; sedimentation rates; vital capacity; qualitative and quantitative sputum examinations, the latter for at least a week before starting treatment; daily temperature and pulse records; and weekly weight determinations.

Very small initial doses of 0.05 g. every five to seven days and increased to 0.15 to 0.20 g. were given. A complete course amounted to 5 to 7 g. After an interval of two to three months a second course and even a third were administered.

Complications were common, especially with reference to abnormal urinary findings. Twenty-five of the 26 cases who received 2 g. or less of the gold showed abnormal urinary findings and 30 of the 32 cases, or 94 per cent, of those who were given 5 to 8 g. of the gold salt had evidence of kidney damage. The predominant abnormal urinary findings in the order of their frequency were the combination of albumin, casts and pus cells; albumin with pus cells; and albumin with casts.

In addition, complications other than renal were also encountered. Of the 26 cases who were given 2 g. or less of the gold salt, which is the smallest quantity given, 15, or 60 per cent, had complications, of which 8, or 30 per cent, had a papular dermatitis; 3, or 12 per cent, had a stomatitis; and 4, or 15 per cent, had a colitis. The dermatitis occurred more often and reached 40 per cent of those who received 8 to 12 g. of the gold salt. Stomatitis was next in frequency and was seen in 6, or 16 per cent, of the 37 cases who were given 2 to 5 g. In this same group 4, or 10 per cent, had colitis.

Neuritis was seen in 2 cases. One patient developed a haemolytic jaundice and one case had a preretinal haemorrhage. Oleosanocrysin, when injected into the buttocks, had a tendency to accumulate unabsorbed at the site of injection and formed a sterile gluteal abscess in some cases. In three instances it was possible to remove the oily solution from the site of the injection one year after the therapy was discontinued.

The urinary findings were transitory and disappeared after discontinuance of the gold therapy. The blood chemistry and kidney function tests showed no variation. However, in one case, the kidney damage proved fatal. The patient was an unfavorable case in an emaciated state, with extensive bilateral cavitation, complicated by a tuberculous laryngitis. His urine before treatment was normal except for an occasional pus cell. Blood chemistry and all kidney function tests were normal. He was given 0.05 g. every five to seven days which was increased to 0.15 g. under the same schedule. When he received 0.75 g. he developed an acute nephritis with nephrosis resulting in anasarca. His urine showed albumin, casts and pus cells. He died one month after discontinuance of the gold salt. Graveson (4) reported 3 fatalities. One case received 2 injections of 0.5 and 0.75 g., respectively. He developed a pleuropneumonia and died. The second patient was given a single course of 3.3 g. The resulting severe dermatitis disappeared but the albuminuria persisted. The patient developed an anuria and died from an acute glomerular nephritis. The third case received 2 courses of gold salt. A haemorrhagic diathesis with subcutaneous ecchymosis resulted in his death. Amberson, McMahon and Pinner (5) report a case of metallic poisoning after receiving 3.9 g. Death was attributed to the toxic effects of the drug.

The other complications mentioned, such as dermatitis, stomatitis, colitis and the miscellaneous complications also disappeared after discontinuance of the gold salt.

In addition, there were constitutional symptoms such as elevation of temperature, streaking, pruritus, headache, loss of weight and nausea and vomiting after the injection.

It may appear strange to present the complications of a drug before acknowledging its therapeutic import. Yet, before deciding the merits of a drug, we must determine the frequency, severity and persistency of the complications produced by that drug.

My series of 110 cases consist of 105 patients with far advanced tuberculosis and 5 with moderately advanced lesions. They include active cases with various

degrees of involvement and diverse anatomical entities. There were exudative, exudative-productive, caseous pneumonic, cavernous, fibrotic, and acinose and acinose-nodose types of lesions. Eight had tuberculous laryngitis. One had *lupus vulgaris* and the other had *tuberculosis cutis orificialis.*

The indications were as follows:

(*1*) Early exudative lesions where collapse therapy was not possible.
(*2*) Far advanced exudative, caseous pneumonic and ulcerative lesions where effective collapse therapy could not be attained.
(*3*) Cases where the involvement was so extensive that collapse therapy was inadvisable.
(*4*) Patients who refused drastic treatment, such as thoracoplasty.
(*5*) Cases with collapse therapy who developed an active lesion in the contralateral lung.
(*6*) Bilateral lesions, in an attempt to clear up one side so that collapse therapy could be instituted for the other side.
(*7*) Cases of fibroid tuberculosis having positive sputum with the hope that the drug might produce a conversion of sputum.
(*8*) Tuberculous laryngitis.
(*9*) *Lupus vulgaris.*

The markedly debilitated, highly allergic patient with a very active and progressive course does not tolerate sanocrysin satisfactorily. Patients with abnormal urinary findings, renal and intestinal tuberculosis, are unsuitable cases.

Of the 110 cases, 84 received from 2 to 14 g. and are suitable for study from a therapeutic standpoint. The remaining 26 are interesting only in so far as complications are concerned. Of the 84 cases, 79 had far advanced lesions and 5 were moderately advanced; 15, or 18 per cent, apparently showed definite improvement and 7, or 45 per cent, of the 15 had sputum conversion. The effect on the laryngeal cases could not be evaluated, as they received other treatment simultaneously, such as silence and cautery. The case of *lupus vulgaris* was definitely temporarily benefited. The gold salt had no value for the patient with *tuberculosis cutis orificialis* who had involvement of the buttocks, perineum and vagina.

The following representative case reports are intended to illustrate the probable influence of gold therapy in those apparently benefited by the administration of the drug.

CASE REPORTS

D. M., age twenty-nine, was admitted to this institution on September 27, 1936, in fair general condition. The onset of his pulmonary tuberculosis was catarrhal, in August, 1936. Examination revealed moderately advanced pulmonary tuberculosis, limited to the upper lobe of the right lung and characterized by an exudative-productive lesion. His sputum was positive. A right phrenic nerve crush was performed on August 26, 1937. Subsequently, there appeared a right basal pneumonic consolidation with very acute symptoms. This was interpreted as a new lesion. Examination also revealed a cavity in the right upper lobe. Two courses of oleosanocrysin were given from November 13,1937 to December 3, 1938, with a total of 6.45 g. of the gold salt. The basal pneumonic process completely disappeared but the cavity persisted. Sputum remained positive.

An attempted right artificial pneumothorax was unsuccessful. A two-stage thoracoplasty, originally refused by patient in August, 1937, was now performed. This resulted in an arrestment of the patient's tuberculosis.

B. J., age twenty-one, was admitted on April 2, 1938, in fair general condition. The onset of her tuberculosis was catarrhal, in October, 1937. Examination revealed far advanced pulmonary tuberculosis, characterized by a large cavity in the right upper lobe and scattered soft infiltrations to the hilum. There was a similar lesion in the left lung. From April 23, 1938 to September 24, 1938 patient was given 3 g. of oleosanocrysin. The therapy was discontinued because of colitis. There was sufficient clearing in the right lung to permit the institution of a left artificial pneumothorax on November 1, 1938. A right artificial pneumothorax was instituted on February 10, 1939. Patient subsequently died from a left spontaneous pneumothorax.

H. M., age twenty-seven, was admitted on February 28, 1938, in fair general condition. The onset of his pulmonary tuberculosis was with a left pleural effusion in 1928. Entrance examination revealed far advanced pulmonary tuberculosis, involving the upper one-half of the right lung and the upper two-thirds of the left lung, characterized by an extensive, fine infiltrative lesion. His sputum was positive. An attempted left artificial pneumothorax was unsuccessful. A right artificial pneumothorax was refused. Patient was given 5.4 g. of oleosanocrysin from March 26, 1938 to November 5, 1938. There was a marked retrogression with almost complete absorption of the lesion in the right lung and considerable retrogession in the left lung. His sputum became negative. He was discharged on June 24, 1940, lesion apparently arrested. He is working and there has been no relapse.

S. H., age twenty-nine, was admitted on July 18, 1933, in fair general condition. The onset of his tuberculosis was catarrhal, in March, 1931. Examination revealed far advanced pulmonary tuberculosis, characterized by a small annular shadow in both upper lobes, with infiltration. In another sanatorium, a right artificial pneumothorax had been instituted and discontinued because of a contralateral spread. His sputum was positive. A right phrenic nerve crush was performed on November 2, 1933, with no diaphragmatic rise nor effect on the lesion. Two courses of sanocrysin were administered from July 7, 1934 to November 24, 1934, and from January 25, 1935 to May 18, 1935, of 6.1 g. and 4.9 g., respectively, making a total of 11 g. There was a disappearance of the annular shadows, clearing of the infiltrations and fibrosis. Sputum became negative. He was discharged on October 5, 1936, lesion apparently arrested. There was no relapse. He subsequently died from a nontuberculous cause.

F. P., age twenty-three, was admitted on October 14, 1933, in good general condition. The onset of his pulmonary tuberculosis was catarrhal, in July, 1933. Examination revealed far advanced pulmonary tuberculosis, characterized by extensive infiltrations in both upper lobes. His sputum was positive. Two courses of sanocrysin were administered from July 10, 1934 to November 24, 1934, and from January 28, 1935 to May 15, 1935, of 5.9 g. and 4.85 g., respectively, making a total of 10.75 g. There was considerable clearing in both lung fields with fibrosis. He was discharged on November 2, 1935, sputum negative, lesion quiescent. He is working and there has been no relapse.

We are aware that similar examples of spontaneous improvement are a common occurrence in pulmonary tuberculosis. Whether the gold salt definitely produced the striking transformation in all 15 cases cannot be stated with certainty.

The behavior of gold in producing the apparently beneficial change is not satisfactorily explained. In 1924 Møllgaard (1) felt that gold penetrates the tuberculous foci, dissolving and disintegrating the tubercle bacilli. The liberated tuberculin produces tuberculin shock. Later, in 1940 Møllgaard (6) stated that the mode of operation of gold is not known for certain. Opinions are divergent. He mentioned that there is a certain affinity existing between sanocrysin and one or more constituent elements of the tuberculous process. Henrichsen and Sweany (2) feel that in spite of its lack of bacteriocidal effect, sanocrysin stimulates all cells entering into the formation of chronic inflammation and healing. Levinson, Petersen and Milles (7) believe that gold first produces a transient stimulation and then an inhibition of the lymph flow, decreasing the permeability of the epithelioid cell layer.

CONCLUSIONS

This presentation is not intended to stimulate nor to recommend the use of sanocrysin in tuberculosis, but to evaluate its efficacy from my personal experience with the drug.

Complications due to sanocrysin are common in occurrence, diverse in distribution, but not persistent and only potentially dangerous. Unfortunately, complications occur very early in the course of treatment before a sufficient amount of gold can be administered to be therapeutically effective. It was found that in the few cases where favorable results were noted, 3 g. or more of the gold salt were given.

The complications *per se* should not deter one from considering gold therapy. There are, however, two factors that place this therapy into disrepute; namely, the lack of substantial proof that gold produces the favorable transformation noted in the few cases apparently helped and the lack of generally accepted scientific evidence to show how gold produced the desired change, if any.

I am inclined to believe that the gold salt in some manner was probably directly responsible for the desired therapeutic result obtained in some of my cases. This cannot be stated unequivocally. A temporary improvement was definitely noted in the patient with *lupus vulgaris*.

The few cases apparently benefited had a predominantly exudative and infiltrative lesion which is the type of tuberculous change that has a greater tendency towards spontaneous retrogression. The extensive caseous pneumonic and ulcerative lesions were unaffected by gold.

It is felt that sanocrysin has no place in the recognized armamentarium for the treatment of pulmonary tuberculosis. However, if all the accepted methods of therapy have been exhausted it might be given a trial from an academic standpoint only, in the suitable case, with the possibility that improvement might occur.

SUMMARY

One hundred ten patients were given gold in the form of sanocrysin and oleosanocrysin; 84 received from 2 to 14 g. and were suitable for study from a therapeutic standpoint; 26 cases were interesting only in so far as complications were concerned. Of the 84 cases, 79 were far advanced and 5 were moderately ad-

vanced. Only 15, or 18 per cent, showed apparent improvement, and 7, or 45 per cent, of the 15 turned negative after gold treatment. Almost all patients showed urinary findings indicative of kidney damage, particularly the combination of albumin with pus cells, albumin, pus cells with casts and albumin with casts. These findings occurred early in the treatment; they were transitory and disappeared after the discontinuance of the gold. One patient, however, developed an acute nephritis and died. Of the extrarenal complications, dermatitis, stomatitis and colitis were the most frequently encountered. Two cases with tuberculosis of the skin have received gold; the one with *lupus vulgaris* was temporarily benefited, while the other with *tuberculosis cutis orificialis* showed no response.

SUMARIO

A 110 pacientes se administró oro en forma de sanocrisina y oleosanocrisina; 84 recibieron de 0.13 a 0.93 gm. y resultaron apropiados para estudio desde el punto de vista terapéutico, pero 26 casos sólo desde el punto de vista de las complicaciones. De los 84 casos, 79 eran muy avanzados y 5 moderadamente avanzados. Sólo 15 (18 por ciento), revelaron mejoría aparente, y 7 (45 por ciento) de los 15 se volvieron negativos con la auroterapia. En casi todos los enfermos los hallazgos urinarios eran indicativos de lesiones renales, en particular la combinación de albúmina con piocitos, albúmina, piocitos con cilindros y albúmina con cilindros. Estos hallazgos correspondieron al principio del tratamiento; fueron muy transitorios y desaparecieron después de suspender el oro. Sin embargo, un enfermo manifestó nefritis aguda y falleció. De las complicaciones externas, las más frecuentes fueron dermatitis, estomatitis y colitis. De dos casos con tuberculosis cutánea que recibieron oro, uno, con lupus vulgar, se benefició temporalmente, mientras que el otro, con *tuberculosis cutis orificialis*, no reveló reacción alguna.

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GASTRIC LAVAGE AND SPUTUM CULTURES[1, 2]

JOSEPH L. ROBINSON AND WILLIAM T. DUNN

The effectiveness of collapse therapy in the treatment of pulmonary tuberculosis has been steadily increasing during the past decade. And with it has come a closer coöperation between the clinician, the surgeon, the roentgenologist and the pathologist. We are all interested in two questions which are assuming more importance as better ways of dealing with them are developed: "Is a pulmonary cavity present?" and "Are tubercle bacilli being expelled from the lungs?" The answers to both can be made with greater certainty now than at any former time. And the improving techniques which are gradually increasing the certainty of the answers are of importance and interest to everyone concerned with the treatment of the tuberculous patient.

Examination of the fasting stomach contents is now generally recognized as an excellent means of determining whether tubercle bacilli are being expelled from the pulmonary passages. When, in 1898, Meunier (1) first suggested this method of examination to obtain sputum from infants and children it aroused little interest. But Armand-Delille's (2) revival of it in 1927 met a different response. Various clinics in Europe began using it, and soon reports of their results appeared in the literature. A chronological listing of published reports is interesting in showing the spread of the use of the procedure throughout the world; a mimeographed copy of such a list may be obtained from the authors.

At first the method was confined to the examination of infants and children. But in 1930 Armand-DeLille (3), in a communication questioning the use of the term "closed tuberculosis," suggested that adults who do not expectorate might well be examined in this manner. Clausen of Denmark (4) seems to have been the first to publish results of its use with adults; his work, dealing with the diagnosis of pulmonary tuberculosis, appearing in 1931. Ulmar and Ornstein (5) some two years later published the first report of its use with adults in this country, at the same time presenting evidence to support the thesis that material can pass up the pulmonary passages and into the oesophagus without conscious expulsion by the individual.

A compilation of the gross results published in the available literature shows a total of 12,040 examinations made, with 36.8 per cent positive results. There were 6,843 examinations of children of which 36.6 per cent were reported positive, and 5,197 examinations of adults of which 37.1 per cent were positive. In addition 903 nontuberculous individuals were examined with one positive result reported. It is quite generally agreed that in most cases tubercle bacilli recovered from the stomach washings indicate the presence of a pulmonary lesion.

The procedure has been in use at Olive View Sanatorium for about two and one-half years (6). During this time various questions regarding technique and

[1] From the Olive View Sanatorium, Olive View, California.

[2] The aid of W.P.A. Project #665-07-S223 is acknowledged.

indications have arisen, and several special studies have been made in an attempt to answer them. The results of our investigations form the basis of this report.

COLLECTION OF MATERIAL

The technique in use at the present time for the collection of the gastric material is as follows: The patient is instructed to refrain from eating or drinking after the evening meal of the day preceding the lavage, which is done sometime between seven and nine a.m. A sterile technique is used throughout. A small calibre, soft rubber tube (Levine), iced and lubricated with a water soluble jelly is passed through one nostril and into the stomach. If it is passed slowly and the subject instructed to swallow as soon as it is felt in the throat, there is very seldom any nausea or difficulty in its passage. We prefer the small nasal tube to the large (Ewald) stomach tube for several reasons. It is easier on the patient,

TABLE 1

Geographical sources in chronological order of published reports on gastric lavage

	BEFORE 1925	1925 TO 1930	1930	1931	1932	1933	1934	1935	SINCE 1935	TOTAL
France	2	1	1	0	3	1	1	1	10	20
Germany		1	1	2	1	1	0	3	1	10
Scandanavia		3	4	4	5	1	4	1	4	26
East Europe			1	0	0	1	0	1	5	8
South Europe				2	1	0	2	4	4	13
Great Britain					1	1	0	0	1	3
South America					2	0	3	0	12	17
North America					2	3	4	0	14	23
Asia							1	0	3	4
Total	2	5	7	8	15	8	15	10	54	124

both psychically and physically. Almost all opposition to the gastric lavage procedure has disappeared from our patients since its adoption. It is safer and produces less trauma of the mucous membrane, and it is easier to pass, so that an adept technician can soon be trained to use it.

As soon as it reaches the stomach any material present is aspirated with a 30 cc. glass (Luer) syringe. This amounts, in most cases, to somewhere between one and two ounces; although it may be less than one or more than eight. Regardless of the amount obtained, one ounce of sterile water is then instilled and immediately withdrawn. Most workers have reported using larger amounts, but this results in such a large bulk that examination of the whole amount is impracticable. We believe it is better to use a small amount of water and examine all the sediment obtained from it than to use a large amount and discard part of it. The claim (8) that the use of fluid for lavage gives fewer positive results than the aspiration of the stomach contents without dilution was studied in 50 cases in the following manner: The stomach contents were aspirated and the

patient given two ounces of water to drink. This was then aspirated and placed in a separate container. Each specimen was treated similarly and examined by culture. In 7 cases, tubercle bacilli were found in the stomach contents and not in the lavage water. But in three instances the water yielded bacilli when the stomach contents did not. This was to us sufficient evidence for making lavage with water a part of the routine examination.

All materials used are thoroughly cleaned and sterilized between cases. But we have not found need for the rigorous technique advocated by some (7). We recognize, of course, the possibility of the presence of acid-fast saprophytes in the stomach contents, but rely on cultural characteristics rather than on morphological appearance to eliminate them. In questionable cases animal inoculation is done.

LABORATORY TECHNIQUE

In the laboratory, the gastric material is added to an equal volume of 4 per cent sodium hydroxide and shaken in a shaking machine for thirty minutes, then neutralized with 10 per cent hydrochloric acid and centrifuged. The supernatant fluid is removed, leaving about 1 cc. of sediment, which is shaken up and studied as follows: 0.1 cc. is spread on a five square centimeter area of glass slide, stained and examined microscopically for acid-fast bacilli. Any found are counted and reported just as are our sputum counts (9). Cultures are made from the remaining material, regardless of the microscopical findings. Saenz-modified-Petragnani and Jensen-modified-Löwenstein media have been used throughout. 0.1 cc. of sediment is planted on each culture medium and at least two cultures on different media are made in each case. The flat-sided one-ounce screw-cap bottles in use at the present time each give the surface area of about three ordinary culture tubes. Few are being spoiled by contamination. A series of 326 showed the following results in that regard:

Both negative	203
Both positive	36
One positive	37
One contaminated	50
Both contaminated	0

The cultures are examined once a week, reported by the end of eight weeks, but kept for six months before being discarded. The interval elapsing before the appearance of a characteristic growth is thirty to sixty days for the majority. A series of 115 positive cases has been tabulated:

Number of days	1–14	15–30	31–45	45–60	Over 60
Number of cultures	1	14	39	47	14

In the majority of cases there were less than ten colonies per culture tube, indicating that small numbers of bacilli are present in the gastric contents of most subjects studied.

Some question may be raised as to our reliance upon the culture method of examining the gastric material. Most writers on the subject of gastric lavage have

indicated their belief in the greater sensitivity of animal inoculation. However, both media and technique have improved during the past few years and the gap between the sensitivity of the two methods has gradually narrowed.

Evidence that culture of the gastric material would yield essentially as many positive results as would guinea pig inoculation was obtained from a study of 209 cases, in which both culture and animal inoculation were made. The guinea pig was positive in 24.4 per cent and the culture in 22.5 per cent. However, in the first 141 inoculations more sediment was used for the guinea pig than for the culture, and the results were: guinea pig positive in 28.4 per cent and culture in 22.7 per cent. But in the last 68 cases more material was used for culture than for the pig, with the result that the pig was positive in only 16.3 per cent while the culture was positive in 22.1 per cent. It seems apparent, then, that the amount of sediment inoculated influences the sensitivity of either method employed.

More positive results might be obtained by using both animal and culture inoculations. Our cases that had both, showed 31.6 per cent positive results as against 30 per cent for the others. However, this increase is not significant. Perhaps the only conclusion which can be drawn is that it is important to inoculate as much as possible of the sediment obtained in culture and/or animal.

RESULTS

In the first 1,000 gastric lavage examinations made at Olive View Sanatorium tubercle bacilli were found in 303, or 30.3 per cent. The total number of persons examined was 738, as there were repeated examinations (one or more) in 189 patients. Thus, 257 patients, or 34.8 per cent, were reported positive. About one-third of the patients examined had reported having "no expectoration." The others had presented sputum which had been found microscopically negative after concentration. More than one-third of these had had, in addition, previous negative sputum culture examinations.

Tubercle bacilli were seen on microscopical examination of the concentrated smear in only 3.9 per cent of the specimens, indicating the small number of bacilli which were present in most cases.

The tests were made, in most instances, at the request of a staff physician; and the patients are thus a more or less selected group. The examination was requested to help establish the diagnosis of pulmonary tuberculosis in 221 newly admitted patients, of whom 29 per cent were positive; to check the results of therapy in 342 patients, of whom 34 per cent were positive; and to confirm X-ray evidence of patent cavity in 70 patients, of whom 47 per cent were positive.

There was a definite decline with increasing age in the frequency of positive results among the males, from 30 per cent in those under twenty to 14 per cent in those over forty. But this was not true among the females.

The stage of the disease showed some influence on the results obtained. There were 66 examinations of material from minimal cases with 23 per cent positive; 411 from moderately advanced patients, with 27.5 per cent positive; and 487 from far advanced cases, with 36 per cent positive.

A definite sex difference was found to exist. The gastric lavage material came from males in 503 instances, with positive findings in 25 per cent; and from females in 497 instances with 36 per cent positive. This difference has been ascribed by some to a so-called esthetic factor which leads more females than males to swallow sputum to avoid expectoration.

Two hundred and ninety-five gastric lavage examinations were made in patients reporting "no expectoration." This condition represents an absolute indication for the use of this procedure, since no sputum is available for study. The tubercle bacillus was demonstrated in 32 per cent of this group; in 25 per cent of 120 males, and 37 per cent of 174 females. The distribution according to age of the patient and stage of the disease showed at least one interesting variation from that of the group as a whole. The 'teen-age females were positive unusually frequently (44 per cent), and this was especially true of those with far advanced disease of whom 65 per cent were positive. After gastric lavage examinations were being commonly employed in the sanatorium, many patients who had never before admitted having sputum began expectorating. This is one of the good side-effects of the use of the procedure; it can be a powerful aid in teaching patients to expectorate and in impressing upon them the danger of swallowing sputum. However, there are undoubtedly many patients in whom small amounts of bacilli-containing mucus is raised and passed into the oesophagus without arousing the cough reflex or causing conscious sensation.

Another group which aroused our interest consisted of 150 patients in whom the X-ray film failed to show cavity and the sputum, if any, was negative. In 23 per cent the stomach contents showed the presence of tubercle bacilli. What is the source of the organisms? A possibility, of course, is tracheobronchial disease. Our records show that 45 of these patients had a diagnosis of tracheobronchial disease, made on the basis of X-ray (10) or bronchoscopic (11) examination or both. Positive reports were had in 29 per cent. There were 105 in whom no such diagnosis was made, with positive reports in 21 per cent. This indicates that the source of the tubercle bacilli was a tracheobronchial lesion in some, but that there must be many instances in which a cavity exists but, because of some reason, such as its small size or being filled with caseous material, does not show on the X-ray film, even with the newer techniques (12).

One hundred and eighty-nine patients had more than one examination, the number varying from two to six. Four hundred and fifty-one tests were made, or an average of 2.4 per patient. The test was positive on one or more occasions in 54 per cent of the group and remained consistently negative in 46 per cent. It is not known on how many the repeated examinations were made for diagnosis and on how many it was repeated after the start of some collapse procedure. It might be mentioned here that, in patients in whom tubercle bacilli were found only by examination of the stomach contents before treatment, any less sensitive form of examination is valueless as a guide to the effectiveness of the treatment. Of the 79 patients in this group who differed to findings, 50 turned from positive to negative and 15 from negative to positive. Eleven alternated, 7 ending with a positive and 4 with a negative report.

There is need for studies of repeated gastric lavage examinations in persons who have an apparently successful pulmonary collapse, together with data as to their later fate. Many of us believe that an effective collapse measure will eventually render the pulmonary excretions entirely free of tubercle bacilli. Such studies would throw considerable light upon this problem and at the same time divulge other information as to the significance of the excretion of small numbers of tubercle bacilli.

Early in our experience with this procedure the question arose as to whether or not patients whose sputa were negative but adequate in amount for study should have gastric lavage examinations. To produce evidence on this question, every patient on whom a gastric lavage examination was requested was asked for a twenty-four hour sputum specimen. This was collected on the same morning that the gastric lavage was done and examined in the same manner: by diges-

TABLE 2

Results by culture of simultaneously collected sputum and gastric material

RESULT OF EXAMINATION	ALL CASES 468		WITH SPUTUM OVER ONE OUNCE 152		WITH SPUTUM UNDER ONE OUNCE 316		WITH NEGATIVE SPUTUM CULTURE 175	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Sputum positive	104	22	42	28	62	20	18	10
With gastric negative	58	12	30	20	28	9	10	6
Gastric positive	133	28	41	27	92	29	37	21
With negative sputum	87	19	29	19	58	18	29	17
Both positive	46	10	12	8	34	11	8	5
One or both positive	191	41	71	47	120	38	47	27

tion, concentration, microscopical search and culture. The patients tested were divided into two groups; those with more and those with less than an ounce of sputum. The results are shown in table 2.

A total of 468 such simultaneous examinations are included in this report. For the group as a whole the sputum and gastric material were both positive in 10 per cent. The sputum was positive in 22 per cent and the gastric in 28 per cent. Tubercle bacilli were found in the sputum and not in the gastric material in 12 per cent and, conversely, in the gastric but not the sputum in 19 per cent. But they were recovered in the sputum and/or the gastric lavage in 41 per cent of the cases examined.

There were 152 cases with sputum exceeding one ounce in amount. In only 8 per cent of these were tubercle bacilli demonstrated in both sputum and gastric material. Yet in six times this number (47 per cent) they were found in one or the other or both the materials. In 28 per cent of the cases the sputum was positive, and in 27 per cent the gastric material was so reported. Tubercle bacilli were found in the sputum and not in the gastric lavage in 20 per cent, and

in the gastric but not in the sputum in 19 per cent. Thus, patients who had rather large amounts of sputum which was microscopically negative yielded no more positive results by gastric lavage examination than by sputum culture. But examination of both materials almost doubled the number of positive results.

Of 316 cases presenting less than one ounce of sputum, tubercle bacilli were found in both material in 11 per cent. A positive sputum was reported in 20 per cent and a positive gastric in 29 per cent. Twice as many (18 per cent) had a positive gastric and a negative sputum as had the reverse condition (9 per cent), and again the percentage of positive findings is larger for the combined group than for either gastric or sputum examinations alone.

Those patients who had had a previous negative sputum culture yielded much fewer positive results than the others. There were 175 such cases in the group. Tubercle bacilli were demonstrated in both materials in 5 per cent, in the sputum in 10 per cent, and in the gastric contents in 21 per cent. The sputum was positive and the gastric negative in only 6 per cent, and the reverse was true in 17 per cent. Consideration of the simultaneous findings raised the total of positive results to 27 per cent.

The findings of tubercle bacilli in both sputum and stomach contents in only 11 per cent of simultaneous examinations is of some significance. It has been reported in the literature (13) that people with a grossly positive sputum give a positive gastric lavage examination in virtually 100 per cent of the cases. This is apparently not true of patients whose sputa contain small numbers of organisms. For in only one-fourth of our positive cases were bacilli recovered from both material. One might conjecture that people who are excreting only a few bacilli daily raise positive material once or twice during the twenty-four hour period and may either swallow or expectorate it. Therefore, in order to increase the likelihood of obtaining that material on any given day, both sputum and gastric contents must be collected. The source of most of the sputum in those individuals who show a negative sputum and a positive gastric may in some cases be the upper respiratory tract, with the small amount of positive material from the lungs being expelled unconsciously into the oesophagus and swallowed.

CONCLUSIONS

1. One thousand consecutive bacteriological examinations of gastric lavage specimens made at Olive View Sanatorium[3] confirm, in general, the efficiency reported in the literature for this procedure as a means of detecting the presence of tubercle bacilli in the pulmonary excretions.

2. We recommend the use of a small calibre, soft rubber tube to collect the material and of small amounts of water for lavage.

3. Inoculation of culture media and/or guinea pigs with as much as possible of the material obtained is necessary for best results. Microscopical examination of the stained sediment is not adequate.

4. Examination by culture and/or animals of simultaneously obtained sputum and gastric lavage material from individuals whose concentrated sputum has

[3]Since the collection of the data for this paper, 3,199 gastric lavages have been done at Olive View Sanatorium, and have further confirmed the conclusions herein reported.

been previously found microscopically negative will yield more positive results than will examination of either material alone.

5. A gastric lavage examination should be made of all individuals who have a negative sputum or no expectoration and are suspected of having pulmonary tuberculosis.

6. It is also indicated in patients under treatment for pulmonary tuberculosis when the sputum becomes scanty or inconstant in amount, or when they cease to expectorate.

CONCLUSIONES

1. Mil exámenes bacteriológicos consecutivos de muestras obtenidas con el lavado gástrico en el Sanatorio Olive View, confirman, en general, la eficacia que se le concede a este procedimiento en la literatura, como medio de descubrir los bacilos tuberculosos.

2. Recomiéndase el empleo de una sonda de caucho blando, de calibre pequeño, para recoger el material, y de pequeñas cantidades de agua para el lavado.

3. Para obtener los mejores resultados se necesita inocular en los medios de cultivo y/o en los cobayos, la mayor cantidad posible del material. El examen microscópico del sedimento teñido no resulta suficiente.

4. El examen en los cultivos y/o en los animales del esputo y el material gástrico obtenido simultáneamente de los individuos cuyo esputo concentrado resultó antes microscópicamente negativo, dará más resultados positivos que el examen de uno u otro material por sí solo.

5. Debe hacerse un examen del material gástrico en todos los individuos cuyo esputo es negativo o no expectoran, si se sospecha que padecen de tuberculosis pulmonar.

6. También está indicada esta técnica en los enfermos en vías de tratamiento por tuberculosis pulmonar, si el esputo se vuelve escaso o varía en cantidad, o dejan de expectorar.

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CULTURES FOR TUBERCLE BACILLI FROM SPUTUM AND GASTRIC CONTENTS[1]

W. STEENKEN, JR., R. L. YAEGER AND F. H. HEISE

Many studies have been made on the correlation of the finding of tubercle bacilli in the sputum and gastric lavage. The stained smear, cultures and animal inoculation methods have been used and correlated. Diagnostic advantages of gastric lavage examination over sputum examinations have been shown in most reports. This report deals with 100 patients whose initial fifty-hour concentrated sputum tests were negative by smear. All were then studied with three consecutive cultures made from fifty-hour concentrated specimens. Of those found negative by this procedure, 33 were studied for three consecutive days with daily culture of their gastric contents and concurrent daily twenty-four-hour sputum specimens. An additional 17 patients were similarly studied for diagnostic reasons.

Of those 50 patients, one was a tuberculosis suspect, 30 had minimal, 14 moderately advanced and 5 far advanced disease; 5 had progressive, 27 retrogressive and 17 stationary disease, as determined by serial roentgenograms. Even after careful instruction as to what constituted sputum, 33 patients denied having any.

METHODS AND TECHNIQUE USED

Gastric lavage method: Levine tubes were boiled and autoclaved at 20 lbs. pressure for one-half hour. The tube was introduced through a nostril with egg oil (non-inhibitory to growth of tubercle bacilli (1)) as a lubricant. With each swallow the tube was encouraged to progress until in the stomach, when gastric contents were aspirated with a 20 cc. B. D. sterile syringe.

Gastric lavages were performed on consecutive mornings, with no food or water allowed during the night and morning preceding lavage. Daily twenty-four-hour sputum specimens were taken at the same time. Sixty per cent of the patients studied denied any noticeable sputum.

Culture method improved (2): Three per cent sodium hydroxide was added in quantity equal to a specimen (sputum or gastric contents) and the mixture was agitated by a shaking machine, that produces 760 three-dimensional shakes per minute (3), for ten minutes before one hour's incubation at 37.5°. It was then centrifuged for ten minutes at high speed, and the resulting sediment adjusted to a slightly acid pH.

One portion was transferred to a small, round-bottom pyrex vial stoppered with a small cork, that contained 5 cc. of a 1:10,000 solution of malachite green. This mixture was agitated in the shaking machine for ten minutes and then centrifuged at high speed for ten minutes. The supernatant fluid was removed

[1] From the Research and Clinical Laboratory, Trudeau Sanatorium, Trudeau, New York.

with a sterile capillary pipette and the sediment suspended in 1 cc. of sterile water.

The second portion of sediment from the first centrifuging was cultured without treatment with dye.

Each suspension, that containing malachite green, as well as the control, was cultured on 2 tubes of Steenken and Smith medium, and on 2 tubes of Hohn's medium. Thus there were: 4 cultures on Steenken and Smith medium, 2 without dye and 2 with inoculum containing malachite green and 4 cultures on Hohn's medium, 2 without dye, and 2 with inoculum containing malachite green.

TABLE 1*

Positive gastric cultures

LABORATORY NUMBER	CULTURE 1				CULTURE 2				CULTURE 3			
	Control		Malachite green 1:10,000		Control		Malachite green 1:10,000		Control		Malachite green 1:10,000	
	Hohn's	S & S	Hohn's	S & S**	Hohn's	S & S	Hohn's	S & S	Hohn's	S & S	Hohn's	S & S
1	—	2	—	2	many	many	many	many	—	—	1	2
2	—	—	1	—	—	—	1	1	—	—	—	—
3	—	—	1	—	—	2	1	1	—	—	—	—
4	1	—	—	—	—	—	—	—	—	—	—	—
5	—	—	—	1	—	—	—	—	—	—	—	2
6	2	—	9	5	—	—	—	—	6	—	4	1
7	—	2	2	5	—	—	—	20	—	—	—	—
8	—	—	—	1	—	—	—	—	—	—	—	—
9	many	many	many	many	many	many	many	many	—	4	8	1
10	—	—	—	—	1	1	—	—	—	—	—	—
11	—	—	—	—	—	—	—	—	1	1	2	3
12	—	—	—	—	1	—	1	1	—	8	1	10

* Figures denote number of colonies found on each slant culture.

** Steenken and Smith's.

RESULTS

Of the 100 patients whose fifty-hour concentrated sputum was negative by staining for tubercle bacilli, 48, a short time later, were shown to have tubercle bacilli in their sputum by one or more of 3 consecutive fifty-hour specimen cultures. The cultures were, however, not uniformly positive; only 17 were positive on all three cultures; 16 on two of the three, and 15 on only one of the three cultures made consecutively.

It is quite evident from this that a microscopically negative fifty-hour concentrated sputum may still contain viable tubercle bacilli demonstrable by culture, and that several consecutive cultures should be made for each examination. Furthermore, in 6 instances out of 52 in which a first series of cultures was negative, subsequent culture series were positive.

Thirty-two of the 100 patients reported developed positive smears two to

four months after the last consecutive culture series. Of these, 16 had no higher than Gaffky II and 16 had a Gaffky III to X.

Of the 50 patients who had simultaneous sputum and gastric lavage cultures, 33 had been included in the above study and found negative. Seven of these 33 were found to be positive on one or more of their gastric lavage specimens when cultured. Three of these 7 were positive a short time later by routine concentration tests. Two of the 7 were positive on all three cultures, 3 were positive on only two of three cultures and 2 were positive on only one of the three cultures.

Eight patients had positive sputum, Gaffky I, just prior to gastric lavage. These were studied by three consecutive simultaneous lavage and sputum smears and cultures with the following results: 4 were negative by lavage and sputum culture, 2 were positive by lavage only and 2 by sputum culture only.

Table 1 is a digest of all positive gastric content cultures, showing the number of colonies found on each slant of Steenken and Smith's medium and Hohn's medium.

DISCUSSION

It was thought that the hydrogen ion concentration of gastric contents might have some effect on the virulence and growth of tubercle bacilli therein. However, analysis showed that most contents containing living tubercle bacilli ranged from pH 3.0 to pH 8.4, with the majority between pH 5.5 and pH 7.5. Inasmuch as the preparation of routine specimens other than gastric contents involves strongly alkaline or acid digestives without greatly affecting the virulence of tubercle bacilli, it seemed unlikely that the pH *per se* of gastric contents had any appreciable effect upon the growth of tubercle bacilli recovered from them. It is possible, however, that specific enzymes, active at a definite pH, may affect the virulence and growth of tubercle bacilli.

To prove their pathogenicity, all culture growths of acid-fast microörganisms that were isolated from gastric contents were inoculated into guinea pigs. All but 2 of the gastric cultures produced tuberculosis. The 2 cultures that remained negative by animal inoculation were isolated from the same patient on two successive culturings. These had the cardinal growth and staining characteristics of the rough type growth of tubercle bacilli. Three additional lavages from this patient failed to produce another positive acid-fast culture, suggesting that the original microörganisms were tubercle bacilli of an attenuated type and that the amount inoculated was not sufficient to produce skin sensivitity to Old Tuberculin. This finding is similar in circumstance to one reported by Sasano, Caldwell, Needham and Medlar (4). They, too, recovered acid-fast microörganisms from diagnostic material that had the cardinal growth and morphology of the tubercle bacillus, but it did not produce disease in guinea pigs.

We have not used concentrated smears for the detection of acid-fast microorganisms from gastric contents, because it was felt that identification of tubercle bacilli by this method was open to question. Recently Baldwin (5) has shown

that acid-fast microörganisms may be recovered from patients, also vegetables and soil that may be classified as saprophytes from their cultural characteristics, and their pathogenicity for guinea pigs, rats, chickens and mice.

This study shows that one must not be satisfied with a single concentrate, culture or gastric lavage, but that each method must be repeated many times if, for any reason, one is to rule out the possibility that the patient is excreting small numbers of tubercle bacilli. In small lesions it is possible that bacilli are excreted only at intervals. Certainly in a patient who denies sputum, or who raises less than 10 cc. daily, it is probable that all expectoration will not contain tubercle bacilli. The failure of consecutive lavage specimens to be uniformly positive point to this conclusion.

In this small series a low Gaffky positive sputum did not necessarily predict a positive culture of the lavage specimen. Indeed, while sputum and gastric lavage may be positive for tubercle bacilli, they may not be positive at the same time as is shown from concurrent specimens.

The failure of gastric lavage to demonstrate bacilli in 2 cases, each with moderately advanced disease, and each having a typical bronchogenic spread to the opposite lung shortly before the test was done, must be mentioned. It is possible, but extremely improbable, that these cases were nontuberculous. Their previous behavior and X-ray pictures were, however, typical and the diagnosis was accepted on each despite the negative lavage. Conversely, patients with pathological areas barely visible by X-ray gave positive cultures. For example, one had a pleurisy with effusion, with only a questionable pulmonary infiltration seen at any time. Another exhibited by X-ray a pathological area smaller than 5 mm. in diameter.

Nearly all in this group of 100 patients denied having any sputum. However, they were encouraged to cough in the early morning, and expectorate into a glass container. Although many specimens looked grossly like saliva they were found positive on culture.

CONCLUSIONS

Concentrated sputum cultures, carefully done, and with selected media, give results that compare favorably with those of gastric lavage.

When tubercle bacilli are difficult to find, persistent and careful bacteriological studies should be made of the sputum and gastric contents, especially by culture and animal inoculation.

The term "negative sputum" should be used cautiously, if at all, when other clinical findings point toward tuberculosis, and it should be qualified by stating the technique by which tubercle bacilli were sought, namely, negative on one concentrated smear; 3 fifty-hour cultures; 3 gastric lavages, *et cetera*.

CONCLUSIONES

Los cultivos de esputo concentrado, debidamente ejecutados y en medios seleccionados, dan resultados que se comparan favorablemente con los del lavado gástrico.

Cuando es difícil encontrar bacilos tuberculosos, conviene verificar estudios bacteriológicos perseverantes y cuidadosos del esputo y del contenido gástrico, en particular por medio de cultivos y de inoculación en animales.

Hay que emplear cautelosamente, si se emplea, el término de "esputo negativo," cuando otros hallazgos clínicos denotan tuberculosis, y hay que precisarlo explicando la técnica empleada para buscar los bacilos, a saber, negativa en un frote concentrado; 3 cultivos a 50 horas; 3 lavados gástricos, etc.

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THE CHORIO-ALLANTOIC MEMBRANE OF THE CHICK EMBRYO AS A MEDIUM FOR TESTING THE VIRULENCE OF TUBERCLE BACILLI[1]

E. W. EMMART AND M. I. SMITH

In an earlier paper (1) it was shown that a marked difference in the incidence of tubercle development occurs in the chorio-allantoic membrane of the chick embryo implanted with strains of tubercle bacilli of different virulence. It was also shown that tubercles developed in the membrane six days after implantation with the suspension of the bacilli, thus presenting a rapid method for determining the virulence of a given strain. In this earlier work two strains of human tubercle bacilli, the more virulent A27 from the Henry Phipps Institute and the less virulent strain H37 from the Saranac Lake Laboratories, were used. In order to ascertain the extent to which this technique might be applied as a method for determining virulence of a strain it was thought advisable to carry this work further using closely related substrains derived from a common stock but differing markedly in virulence. The present paper presents data obtained from the implantation of the two substrains of H37, substrain Rv (virulent) and Ra (avirulent), which were furnished us by Mr. W. Steenken of the Trudeau Laboratories at Saranac Lake. These strains first isolated by Steenken and associates in 1934 (2) are reported to maintain an unaltered degree of virulence to the present time when grown on Proskauer and Beck medium (3).

METHODS

In order to check the relative virulence of the two substrains H37-Rv and H37-Ra, suspensions were implanted on the chorio-allantoic membrane of the nine-day chick embryo and also inoculated into guinea pigs. Homogeneous suspensions for injection were prepared in physiological salt solution from cultures three to five weeks of age. The cultures were carefully lifted from the surface of the medium, weighed with sterile precautions and diluted in the salt solution to make a 0.5 per cent suspension. Thirty minutes rotation in a White bacteria grinder produces a homogeneous opalescent suspension. A circular disc was drilled out of the shell above the membranes adjacent to the embryo and near the large end of the egg. Two-tenths of a cc. of the suspension was placed on the chorio-allantoic membrane thus implanting each egg with 1.0 mg. of tubercle bacilli, moist weight. Other details of the technique for inoculation were identical with those previously described (1). Six days after inoculation the membranes were exposed, observations made and the tissue fixed *in situ* with 10 per cent formalin for fifteen minutes. The membranes were then cut out and fixed in Zenker-formol. Sections were stained with Ziehl-Neelsen and Giemsa stains and the sectioned membranes studied for incidence and extent of cellular proliferation and tubercle formation. The proliferation of the outer

[1] From the Division of Chemotherapy, National Institute of Health, U. S. Public Health Service, Bethesda, Maryland.

epithelium, the incidence of the eosinophilic and monocytic proliferation and the degree of development of the tubercles were noted. Each of these were graded from 0 to 4 and the average determined for each experiment. The details of the method of evaluation are shown in table 2 for experiments 61 and 62.

To determine the relative virulence of the two strains in guinea pigs, the animals were inoculated intraperitoneally with 0.5 mg. of tubercle bacilli, moist weight, suspended in 1 cc. of physiological saline. The animals were weighed once a week. Upon death all were autopsied and the incidence of tubercle development evaluated in the lungs, omentum, liver, spleen and peritoneum.[2] Each was graded from 0 to 4 and the total for all 5 organs or tissues added to obtain the tuberculosis index for each animal. A score of 20 was the maximum degree of infection that could have been present in any one animal.

RESULTS

Development of tubercles in the chorio-allantoic membrane of the chick embryo: Considerable variation may occur in the size and number of tubercles in any series of membranes inoculated with the same suspension. This might be expected since the eggs were obtained commercially from a pooled supply and not from selected hens of inbred stock. In membranes inoculated with the virulent H37-Rv, tubercles may be found in all stages of development (plate I, figures 4, 5, 6). They are readily visible proliferating downward toward the inner surface of the membrane. They are grossly visible first as small pinpoint opacites or thickenings either as isolated patches or in clusters. These latter areas finally become large conglomerate tubercles (plate I, figures 4 and 5). With the avirulent strain many membranes show no gross tubercles, a few show tubercles just forming and an occasional one shows a single isolated minute tubercle (plate I, figures 1, 2, 3). Membranes inoculated with H37-Rv showed an average of 96 per cent tubercle formation, while those inoculated with H37-Ra gave only 18 per cent tubercle formation. None of the tubercles in the latter series was either large or necrotic (table 1).

Microscopical examination of the membranes shows thickened areas of the surface epithelium. This is caused by physical or chemical injury or both. Mechanical injury alone usually results in thickening of the outer epithelial membrane, with squamification of the cells and not infrequently with necrosis of the outer surface. In addition to these changes chemical injury may also produce small areas of hyperplasia of the outer membrane. The change in the surface epithelium may exist independently of the process of tubercle formation. However, when an average is taken of the degree of cellular proliferation of the epithelium of the membranes implanted with the two strains of bacilli, the difference in degree of proliferation is significant (table 1, column 1).

All implantations of the membranes are accompanied by an increase in the number of eosinophils in the membrane. This appears to be a characteristic inflammatory reaction which in this instance also accompanies monocytic pro-

[2] The kidneys, which showed a relatively low incidence, were grouped with the peritoneum.

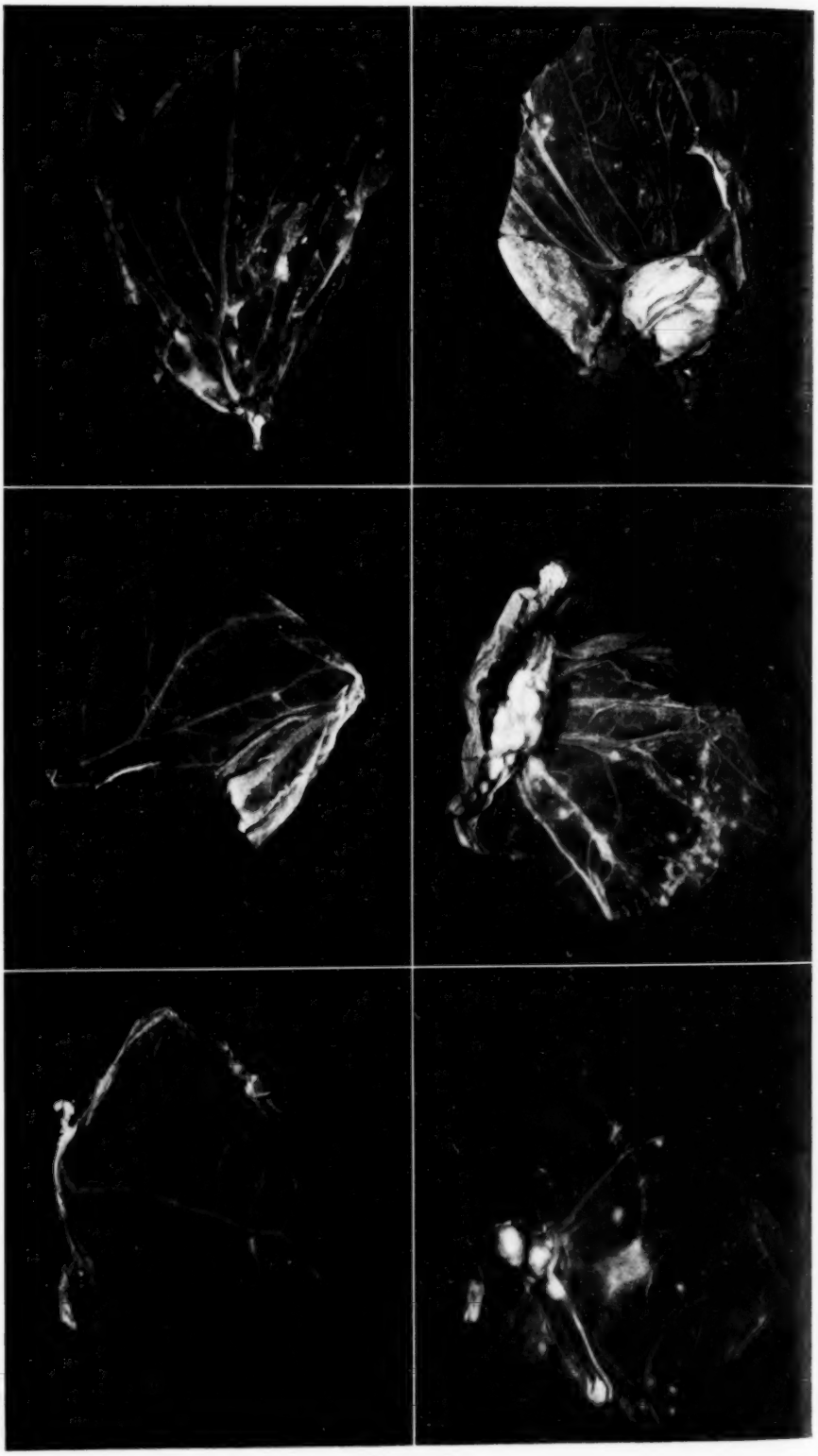

PLATE I

TABLE 1

Comparison of the degree of cellular proliferation of membranes inoculated with H37-Rv with those inculated with H37-Ra

EXPERIMENT NUMBER	NUMBER OF EGGS INOCULATED	NUMBER OF EGGS SURVIVING	PER CENT GROSS TUBERCLES	MICROSCOPICAL OBSERVATIONS			
				Average degree of cellular proliferation and aggregation on the basis of 0 to 4			
				Epithelial thickening (1)	Eosinophils (2)	Monocytes (3)	Degree of development of tubercles (4)
I. Membranes inoculated with substrain H37-Rv							
46	24	10	90.0	1.0	2.3	3.0	1.6
60	18	10	100.0	1.4	2.8	2.8	2.6
61	21	5	100.0	3.0	3.0	3.0	3.0
Average			96.6	1.8	2.7	2.9	2.4
II. Membranes inoculated with H37-Ra							
47	30	14	25.0	0.8	1.3	1.0	0.2
62	36	10	20.0	0.6	0.9	1.0	0.1
64	42	21	9.0	0.9	1.0	1.4	0.1
Average			18.0	0.7	1.1	1.1	0.1

liferation and aggregation. A comparison of the average number of eosinophils present in the membranes implanted with the two strains shows that they are more than twice as numerous in the membranes implanted with the virulent strain as those implanted with the avirulent one.

The large number of eosinophils which are seen in the sections may be accounted for partly by the fact that normally in the blood of the adult fowl the

FIG. 1 (upper left). Membrane after inoculation with H37-Ra, showing a few minute tubercles.

Experiment 62, egg 18, magnification approximately × 1.3.

FIG. 2 (center left). Membrane after inoculation with H37-Ra, but showing no abnormality.

Experiment 62, egg 12, magnification approximately × 1.3.

FIG. 3 (lower left). Membrane after inoculation with H37-Ra, but showing no abnormality.

Experiment 62, egg 13, magnification approximately × 1.3.

FIG. 4 (upper right). Membrane after inoculation with H37-Rv shows large conglomerate tubercle.

Experiment 60, egg 12, magnification approximately × 1.3.

FIG. 5 (center right). Membrane after inoculation with H37-Rv, showing numerous discrete tubercles and large conglomerate tubercle.

Experiment 60, egg 10, magnification approximately × 1.3.

FIG. 6 (lower right). Membrane after inoculation with H37-Rv, showing discrete and conglomerate tubercles.

Experiment 60, egg 8, magnification approximately × 1.3.

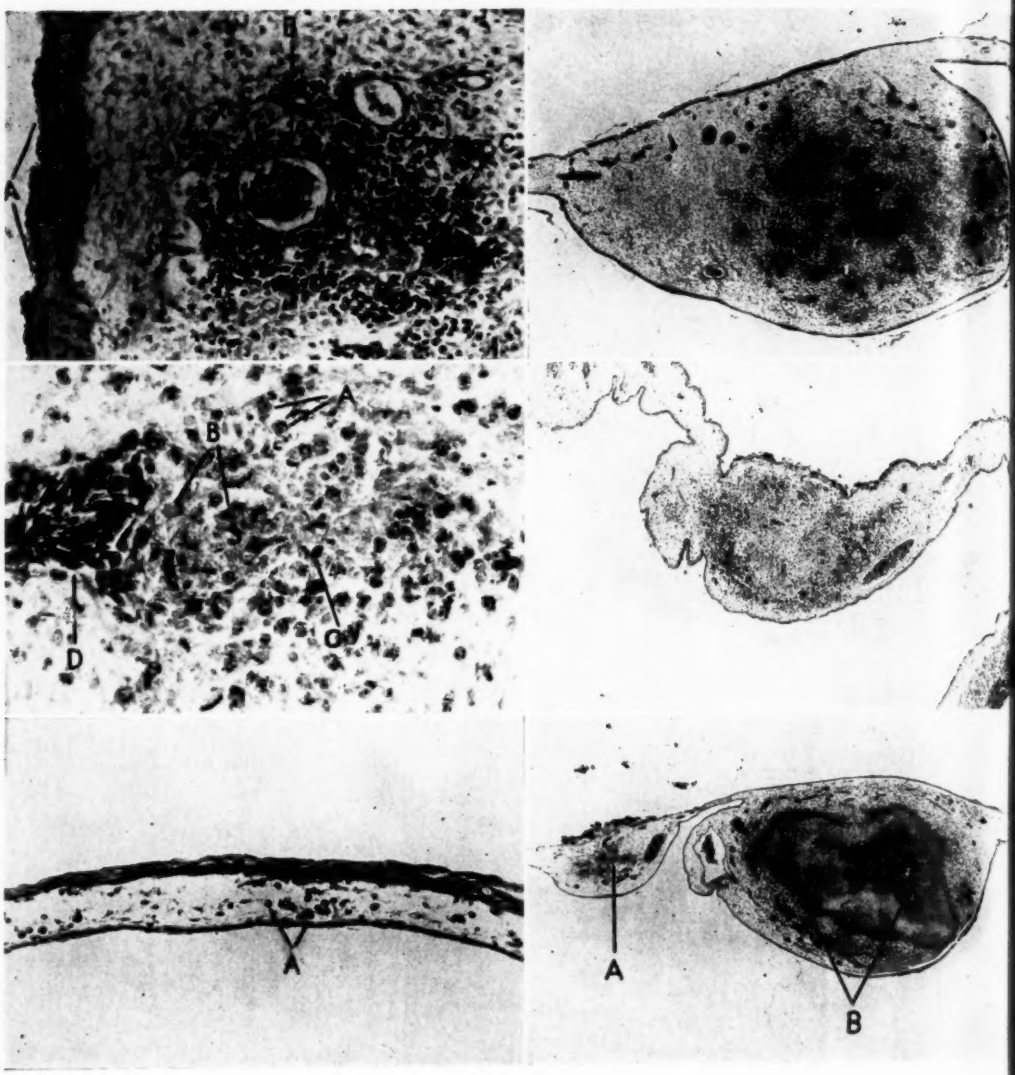

PLATE II

FIG. 1 (upper left). Tubercle developing near blood vessel.

A. Lower epithelial membrane

B. Blood vessel

C. Aggregation of monocytes and eosinophils

Experiment 61, egg 19, inoculated with tubercle bacilli H37-Rv, magnification × 249.

FIG. 2 (center left). Grouping of monocytes and eosinophils around clumps of tubercle bacilli of H37-Rv strain.

A. Eosinophils

B. Monocytes

C. Clump of bacilli

D. Blood vessel

Experiment 61, egg 19, magnification × 570.

eosinophils are 50 per cent of the total polymorphonuclear leucocytes while only 10 per cent are monocytes (4). After the ninth day, the embryonic blood count of the embryo resembles, to a large extent, that of the adult fowl. Since the embryos were examined on the fifteenth day, the preponderance of eosinophils in blood smears was readily observable. In sections of the chorio-allantoic membrane they may be scattered throughout the membrane or in clusters usually near the blood vessels.

The most significant cellular change which follows implantation of the membrane with tubercle bacilli is the multiplication and aggregation of the monocytes (plate II, figure 1) which mark the beginning of tubercles. Bacilli are usually present wherever these aggregates of monocytes appear in the membrane (plate II, figure 2). Following implantation with the avirulent strain of bacilli most of the membranes appear normal (plate II, figure 3) and the typical tubercle with compact centres with necrosis and caseation is rarely seen. In such membranes the tuberculous nodule, when present, is little more than an aggregate of monocytes infiltrated with connective tissue fibrils. When virulent strains are implanted on the chorio-allantoic membrane, tubercles in all stages of development are found. They arise in dense clusters of monocytes and eosinophils frequently near a blood vessel (plate II, figure 1). A number of tubercles may begin to develop adjacent to each other and these develop into large conglomerate tubercles (plate II, figure 4) which eventually undergo caseation and necrosis (plate II, figures 4 and 5). These areas frequently develop homogeneous, compact centres which eventually become caseous and necrotic (plate II, figure 6). The central part of the tubercle stains readily with acid fuchsin and is usually fringed with basophilic monocytes.

A comparison of the average monocytic index for membranes implanted with virulent and avirulent strains of H37 shows the value for the membranes implanted with the virulent strain of bacilli to be more than twice that of the avirulent strain (table 1, column 3).

A similar evaluation of the degree of development of the tubercles in the membranes inoculated with both the virulent and avirulent strains shows a marked difference in tubercle incidence, the tubercle development in membranes implanted with virulent bacilli being more than twenty times as great as those implanted with H37-Ra (table 1, column 4).

FIG. 3 (lower left). Section of membrane inoculated with H37-Ra.

A. Few scattered monocytes

Experiment 62, egg 18, magnification × 249.

FIG. 4 (upper right). Section through conglomerate tubercle after inoculation of chorio-allantoic membrane with H37-Rv strain.

Experiment 60, egg 8, magnification × 27.

FIG. 5 (center right). Discrete tubercle after inoculation with H37-Rv with caseation necrosis beginning in centre.

Experiment 61, egg 16, magnification × 27.

FIG. 6 (lower right). Section showing small tubercle in early formation (A) and one large conglomerate (B) with caseous and necrotic centre. Membrane inoculated with H37-Rv.

Experiment 60, egg 12, magnification × 18.

TABLE 2

Comparison of the degree of tuberculosis development, gross and microscopical, in chorio-allantoic membranes inoculated with H37-Rv (Exp. 61) and H37-Ra (Exp. 62)

Degree of cellular proliferation graded 0 to 4

EGG NUMBER	(1) GROSS TUBERCLES	(2) EPITHELIAL PROLIFERATION	(3) EOSINOPHILS	(4) MONOCYTIC PROLIFERATION AND AGGREGATION	(5) DEGREE OF TUBERCLE DEVELOPMENT
Experiment 61—Inoculation with H37-Rv					
2	++	+++	+++	+++	++
10	++++	+++	+++	+++	+++
11	++++	+++	++	++	++
13	++++	+++	++++	++++	++++
19	++++	+++	+++	+++	++++
Average.....	3.6	3.0	3.0	3.0	3.0
Experiment 62—Inoculation with H37-Ra					
1	−	+	+	+	−
8	−	−	−	−	−
9	+	−	+	+	+
12	−	+	+	+	−
13	−	−	+	+	−
15	−	−	+	+	−
18	−	+	+	+	−
20	+	+	+	+	−
30	−	+	+	+	−
35	−	+	+	++	−
Average.....	0.2	0.6	0.9	1.0	0.1

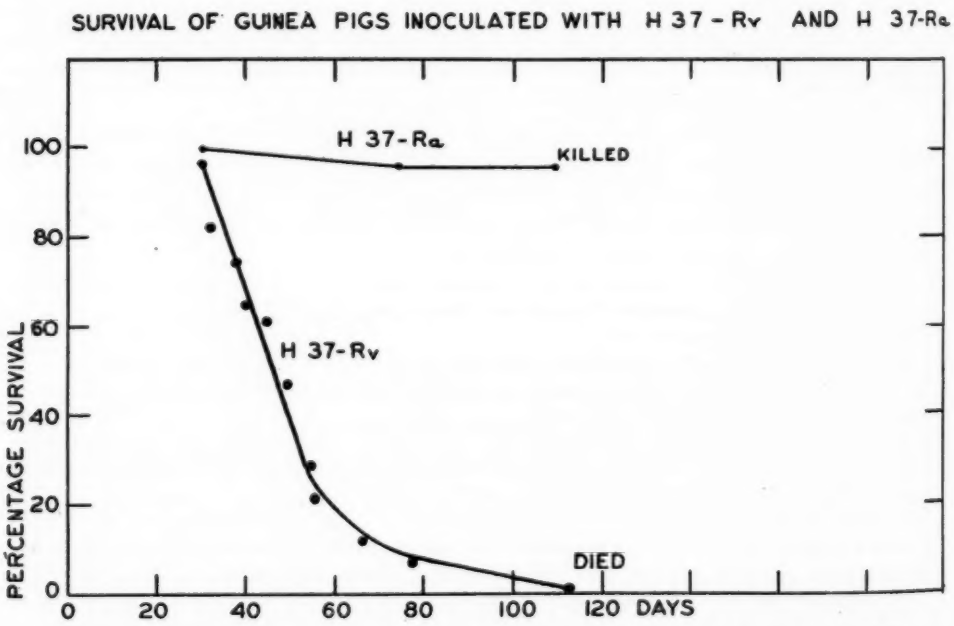

CHART 1. Survival of guinea pigs inoculated intraperitoneally with H37-Rv and Ra

A comparison of two experiments of membranes implanted with the virulent H37-Rv and avirulent H37-Ra strains is shown in detail in table 2, giving the difference in degree of invasiveness and pathogenicity of the two strains.

Inoculation of H37-Rv and Ra into guinea pigs: In order to verify the difference in virulence of the two substrains H37-Rv and Ra after cultivation in this laboratory for six months, 28 guinea pigs, 300 to 400 g. each, were inoculated intraperitoneally with 0.5 mg. moist weight of H37-Rv and 16 with Ra. After forty days, 36 per cent were dead of those inoculated with the virulent strain, at sixty days 85 per cent and at one hundred and twelve days all were dead. Of the 16 guinea pigs inoculated with Ra, one died at seventy-four days and all the rest were killed at 109 days (chart 1).

The average tuberculosis index for guinea pigs inoculated with H37-Rv was 11.9 while those inoculated with Ra had an index of only 0.8, a ratio of approximately 15 to 1. Of the guinea pigs inoculated with H37-Ra, 5 had no gross evidence of tuberculosis, 9 had a value of 1 and 2 had a value of 2.

From the evidence obtained both from the experiments with chick embryo membranes and guinea pigs it may be concluded that there is a marked difference in the virulence of the two substrains H37-Ra and Rv, and that this difference is distinguishable equally well by the chorio-allantoic method and the guinea pig inoculation method.

CONCLUSIONS

Within six days after implantation of the chorio-allantoic membrane of the chick embryo, 96 per cent tubercle formation was present in the membranes implanted with the strain H37-Rv, while only 18 per cent tubercle formation was present in those implanted with the avirulent strain H37-Ra.

Corresponding differences in invasiveness of the two substrains were found in guinea pigs. Only one guinea pig inoculated with H37-Ra died within one hundred and nine days, while 100 per cent of those inoculated with H37-Rv died within the same period. This demonstrates that the chorio-allantoic membrane of the chick embryo can be successfully used to determine differences in virulence between closely related substrains of tubercle bacilli.

CONCLUSIONES

A los seis días de sembrarse la membrana corio-alantoica del embrión de pollo, la formasión de tubérculos representaba 96 por ciento en las membranas en que se sembró la cepa H37-Rv, comparado con sólo 18 por ciento en aquéllas en que se sembró la cepa avirulenta H37-Ra.

En los cobayos se observaron diferencias correspondientes en la facultad invasora de las dos subcepas. Sólo un cobayo inoculado con la H37-Ra murió dentro de 109 días, comparado con 100 por ciento de los inoculados con H37-Rv, lo cual demuestra que puede emplearse con éxito la membrana corio-alantoica del embrión de pollo a fin de determinar la diferente virulencia de las subcepas afines de bacilos tuberculosos.

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BRONCHIECTASIS AND DEXTROCARDIA[1]

Observations on the Aetiology of Bronchiectasis

ARTHUR M. OLSEN

Some years ago Kartagener (14) called attention to the frequency with which bronchiectasis and sinus disease accompany transposition of the viscera. The simultaneous occurrence of these three conditions occasionally has been called "Kartagener's triad." The frequency of occurrence of this syndrome has served as a powerful argument in favor of the theory of the congenital origin of bronchiectasis.

In an attempt to shed further light on the subject of the pathogenesis of bronchiectasis, a study has been made of the incidence of bronchiectasis among patients who had congenital dextrocardia. It is generally recognized that bronchiectasis and disease of the accessory nasal sinuses occur very commonly together, and for the purpose of this paper the incidence of sinus disease is considered to be of secondary importance.

During a period of twenty-two years, 1920 to 1941, inclusive, a total of 85 patients who had true congenital dextrocardia were encountered at the Mayo Clinic. The congenital nature of the dextrocardia was proved in each instance by roentgenological study of the thorax and was confirmed in the great majority of patients by one of the following diagnostic tests: electrocardiography, roentgenological examination of the stomach, roentgenoscopic study of the colon, surgical exploration, bronchoscopy or postmortem examination. In all instances in which additional studies were carried out, it was readily demonstrated that complete transposition of all the viscera was present. All cases in which the possibility of acquired dextrocardia was suggested were omitted from the group.

Definite evidence of bronchiectasis was present in 14 (16.5 per cent) of the 85 patients. For 5 patients the diagnosis of bronchiectasis was established by bronchographic or bronchoscopic means. Among the remaining 9 patients, bronchiectasis was so far advanced that the clinical features, including the history, results of physical examination and postural drainage and of examination of the sputum, and stereoroentgenograms made the diagnosis obvious. Definite evidence of disease of the accessory nasal sinuses was present in 10 of the 14 cases. It is of interest to notice that sinus disease also was present among an additional 4 patients who had dextrocardia but in whom convincing evidence of bronchiectasis was not present.

In the twenty-two year period under consideration a diagnosis of bronchiectasis was made in less than half of 1 per cent of the total number of patients who registered at the Mayo Clinic. When this figure is compared with the 16.5 per cent incidence of bronchiectasis among patients who had congenital dextrocardia, it is readily apparent that the relationship between dextrocardia and bronchiectasis is hardly coincidental. Statistics concerning the relative fre-

[1] From the Division of Medicine, Mayo Clinic, Rochester, Minnesota.

quency of this combination as presented in this paper are roughly parallel to those presented by Adams and Churchill (1) (21.7 per cent) and Kartagener and Horlacher (20 per cent).

Adams and Churchill have summarized the literature concerning Kartagener's syndrome. It may be worth while, however, to enumerate briefly the reported instances of bronchiectasis and *situs inversus*. Kartagener and Kartagener and Horlacher (15, 16) have reported a total of 11 cases. Adams and Churchill presented 5 cases. Nüssel and Helbach (18) have accounted for 2 instances. Single cases have been reported by Siewert (22), Oeri (19), Guenther (11), Casaubon and Derqui (7), Behrmann (6), Wernli-Haessig (23), Glaum (10), Rosenthal (21), Becker (5), Ingraham (13), Nagy (17), Cole and Nalls (8) and Adland and Einstein (3). The total cases reported number 31. Adding the 14 cases of the present series, there are now 45 instances of the syndrome on record.

Practically all authorities who have reported instances of this symptom complex are in agreement that the frequency of bronchiectasis among patients who have dextrocardia lends support to the theory of the congenital origin of the disease. Adams and Churchill, who offered the first reports of this syndrome written in the English language, have presented a scholarly discussion of the embryological and environmental factors that influence the development of congenital anomalies. They concluded that two types of people are affected by transposition of the viscera. First, a person who has *situs inversus* may be otherwise entirely normal; such a person is a mutant. On the other hand, the transposed viscera may represent part of a process of maldevelopment which, in association with other congenital defects, makes the person a monster. Adams and Churchill suggested that bronchiectasis in association with dextrocardia represents a stigma of maldevelopment. With these speculations in mind, analysis of the associated congenital anomalies in the present group of cases was made. Eleven of the 85 patients with dextrocardia had other defects that included congenital heart disease, hydrocephalus, imperforate anus, cleft palate, twelve fingers, flail thumb and others. In addition, 2 of the patients had cardiospasm. It is interesting to observe that none of the 14 patients with bronchiectasis had any other defects. It seems likely that all patients who have transposition of the viscera, either with or without other anomalies, have undergone some peculiarity of development. The presence of other defects would constitute varying degrees of deviation from the normal.

There has been much discussion concerning the aetiology and pathogenesis of bronchiectasis. European authorities have long favored the congenital theory of origin which I previously mentioned. Results of studies such as the present one would seem to lend support to this theory. The occurrence of bronchiectasis in identical twins also has been reported and recently was the subject of a communication by Pastore and me (20). The detection of instances of so-called dry bronchiectasis is by no means uncommon. There must be many persons with bronchial dilatation who are entirely symptom free. In many cases such bronchial dilatation may have been present since birth. Attention will be called to these people only if haemoptysis occurs or if the bronchi become in-

fected. Strictly speaking, bronchiectasis means "bronchial dilatation." The commonly described symptoms of bronchiectasis are actually those of one of its complications; namely, infection of the ectatic bronchi. Supporters of the congenital theory of origin of bronchiectasis believe that bronchial infection is a result rather than a cause of the clinical syndrome as it is generally known.

The prevailing opinion among American authorities is that in the great majority of instances bronchiectasis is acquired. It is not within the scope of this paper to review the extensive literature pertaining to this subject. However, it may be said that there are two outstanding concepts of the pathogenesis of acquired bronchiectasis: first, that bronchiectasis is the result of bronchial obstruction with its associated phenomena; and second, that atelectasis in itself is the precipitating factor. The usual explanation is somewhat as follows. A partial or perhaps complete bronchial obstruction due to a foreign body, thick secretions, tumor or inflammatory bronchial stenosis, results in retention of bronchial secretions. These secretions become infected and give rise to a chronic inflammatory process in the walls of the bronchi. The elastic fibres are destroyed and the walls are weakened. Distention of these bronchi by retained secretions, cough and forced inspiration results in bronchial dilatation. Adams and Escudero (2) were able to produce bronchiectasis experimentally by partially obstructing a bronchus and introducing infected material into the bronchial tree. The bronchiectasis that may follow inhalation of a foreign body or a patient's postoperative aspiration of infected material can be explained readily on the basis of the aforementioned mechanism. Inflammatory bronchial stenosis in association with acute pulmonary diseases, such as pneumonia, may result in bronchiectasis. Holinger (12) has called attention to this type of bronchial obstruction and has emphasized the necessity for bronchoscopic examination in cases of so-called unresolved pneumonia.

Andrus (4) has expressed the view that pulmonary atelectasis is the aetiological factor in bronchiectasis. Fleischner (9) has presented evidence in favor of this conception. These authors believed that bronchiectasis occurs in the collapsed portion of the lung. According to this theory, the movements of functioning pulmonary tissue exert an elastic pull on the bronchi in the atelectatic portion of the lung, thus producing bronchial dilatation. Deficient ventilation in the newborn infant creates a picture of patchy atelectasis which may result in bronchial dilatation. Superimposed infection later in life leads to bronchorrhoea. According to this view, congenital pulmonary atelectasis is the real cause of so-called congenital bronchiectasis. The inhalation of carbon dioxide or the use of other means of stimulating respiration should therefore prevent congenital bronchiectasis.

Seven of the 14 patients who had both bronchiectasis and dextrocardia in this reported series stated that they had had symptoms as long as they could remember. Among the remaining 7, clinical evidence of bronchiectasis developed in the adolescent or adult periods of life, and bronchorrhoea developed after tonsillectomy or pneumonia among 5 of these 7 patients. It seems reasonable to assume that these 14 patients were born with bronchial dilatation or with weak-

walled bronchi which lacked the proper kind of elastic tissue. Yet external factors were necessary for the development of clinical bronchiectasis in at least half of the cases. Infection must be introduced before a chronic, productive cough develops.

COMMENT

Clinical experience demonstrates that the manifestations of bronchiectasis most often appear after the precipitating factors of bronchial obstruction, atelectasis and bronchial infection. Such aetiological influences, however, are more likely to provoke the clinical syndrome in persons whose bronchi are peculiarly susceptible to dilatation than among others. The frequency with which bronchiectasis occurs among persons who have transposition of the viscera, its occurrence in twins and siblings and the increasing recognition of asymptomatic or dry bronchiectasis would seem to indicate that maldevelopment of the bronchial walls may be a primary factor in the pathogenesis of bronchiectasis. Thus, both congenital and acquired components probably enter into the production of most instances of the disease.

SUMMARY AND CONCLUSIONS

1. During a period of twenty-two years, 85 patients who had congenital dextrocardia were seen at the Mayo Clinic. Fourteen (16.5 per cent) of these patients also had bronchiectasis. The incidence of bronchiectasis among patients who have registered at the clinic is less than half of 1 per cent.

2. A review of the literature disclosed that 31 similar cases had been reported previously.

3. The frequency with which bronchiectasis accompanies visceral transposition lends support to the theory of the congenital origin of many instances of bronchiectasis.

4. A consideration of the evidence in favor of both the congenital and acquired theories of the origin of bronchiectasis would seem to indicate that both congenital and acquired components enter into the production of most instances of the disease.

SUMARIO Y CONCLUSIONES

1. En la Clínica Mayo han sido observados en un período de veintidós años 85 enfermos que manifestaban dextrocardia congénita. De ellos, catorce (16.5 por ciento) tenían además bronquiectasia. La frecuencia de la bronquiectasia entre los enfermos inscritos en la clínica es inferior a la mitad de 1 por ciento.

2. Un repaso de la literatura reveló que se habían descrito antes 31 casos semejantes.

3. La frecuencia con que la bronquiectasia acompaña a la transposición visceral presta apoyo a la teoría del origen congénito de muchos casos de bronquectasia.

4. El estudio de los datos en pro, tanto de la teoría congénita como la ad-

quirida, del origen de la bronquectasia, parece indicar que ambos factores intervienen en la producción de la mayor parte de los casos.

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Horton Ryan Casparis

1891–1942

Dr. Horton Ryan Casparis—pediatrician and public health statesman—died suddenly of a heart attack in his hotel room in Richmond, Virginia on November 11, 1942, while attending a meeting of the Southern Medical Association. This man died at fifty-one, in the very prime of his very busy life. He was Professor of Pediatrics in Vanderbilt University and head of the Department, and he had an active and effective hand in many constructive projects and agencies for good—agencies which contemplated child welfare, mental hygiene and education, the combating of tuberculosis, the fowarding of scientific research.

Born in Round Mountain, Texas, on March 15, 1891, Doctor Casparis passed through the local schools and received his A.B. degree from the University of Texas in 1915. He proceeded in the same year to Baltimore where he entered the Johns Hopkins Medical School, from which he was graduated as Doctor of Medicine four years later. He manifested an early interest in study as shown by his first medical publication (on the lymphatics of the omentum) which appeared during his student days.

In the year of his graduation from Medical School, Doctor Casparis developed pulmonary tuberculosis and spent many months under treatment at Trudeau Sanatorium. His disease was extensive but his recovery complete. Toward the end of his stay at Trudeau, phlyctenular conjunctivitis plagued him for a while. However, he handled his infection so well that he was enabled to return to the Johns Hopkins Hospital and spend four uninterrupted years of active hospital life as Interne, Assistant Resident and Resident in the Department of Pediatrics, meantime serving as Instructor and Associate in this Division. These appointments he gave up to assume charge of the reorganized Department of Pediatrics at Vanderbilt University.

The zest for research shown in student days found an increased stimulus and a field of fruitful effort during the months at Trudeau, for Doctor Casparis developed a lively interest in tuberculosis which he maintained throughout his life and which yielded at least eleven items in his rather extensive bibliography. His writings attest and reflect his wide interests and study which touched always, either scientifically or sociologically, on the health and welfare of children.

From north, south, east and west came invitations to attend meetings and to take places on programs. He presented his material with an informality unusual in the guest speaker. Whether before a group of pediatricians, tuberculosis workers, educators or other laymen, his topic was timely and to the point. But he found it a heavy chore to prepare the substance of his discourse for publication—with the result that his list of writings is much less extensive than it could well have been. This knack of putting his thoughts over from the lecture platform attests his worth as an educator. This applies particularly to his contact with organizations of practicing physicians. One of his closest friends

has pointed to his "capacity to make complex things simple" as his most conspicuous characteristic and greatest asset.

His absorbing interest in pediatrics and his ability to think in his chosen specialty led to an ever enlarging field of endeavor. He served as Chairman, Section on Pediatrics of the American Medical and the Southern Medical Associations; Chairman, Advisory Committee, U. S. Children's Bureau; President, American Board of Pediatrics; Chairman, Tennessee State Nutrition Committee. He had membership in the National Maternal and Child Health Council; Mental Health Committee, American Academy of Pediatrics; "Advisory Panel," National Assocation of Nursery School Education; and Editorial Board, American Journal of Diseases of Children. In all these contacts and endeavors he was a quiet, potent catalyst.

Horton Ryan Casparis
1891-1942

In the field of tuberculosis he served as President of the Southern Conference, the Tennessee Tuberculosis Association and the southern section of the American Trudeau Society; as Director of the National Tuberculosis Association and member of its Executive Committee and, also, as member of the Council, American Trudeau Society.

The weight of his influence on the speaker's stand, on the printed page and in committee deliberations was great. He lived a busy and useful life, serving the broad interests of child health and the public health of the nation. His death is a heavy loss, but he leaves an enviable heritage to his family and profession.

HENRY STUART WILLIS

AMERICAN TRUDEAU SOCIETY

Report of the Committee on Standard Laboratory Procedure[1]

Dr. H. S. Willis, *Chairman*
Dr. Emil Bogen — Dr. Henry C. Sweany
Dr. Max Pinner — Dr. Arthur J. Vorwald

STAINING OF TUBERCLE BACILLI IN TISSUE

It is often desirable to apply a stain for detection of tubercle bacilli in tissue preparations. This is especially so in lesions where the histopathology is not pathognomonic for tuberculosis, or in cases where tubercle bacilli had never been found in the sputum. The following procedure is highly recommended for further trial.

Fixation: Thin blocks of tissue are immersed in a generous amount of fixing fluid for from twelve to twenty-four hours. A good fixing agent is Zenker's fluid to which acetic acid or formalin is added just before using.

Zenker's Fluid

Potassium bichromate	2.5 g.
Mercuric bichloride	5.0 g.
Water	100 cc.

Acetic-Zenker Fluid

Zenker's fluid	95 cc.
Glacial acetic acid (add when using)	5 cc.

Formalin-Zenker Fluid

Zenker's fluid	90 cc.
Neutral formalin (add when using)	10 cc.

(Formalin is neutralized by adding magnesium carbonate, shaking vigorously and allowing the carbonate to settle out.)

Formalin (10 per cent) is not a satisfactory fixing agent for tissues to be stained for tubercle bacilli because it has the tendency to lessen the affinity of the bacilli for the dye.

Blocks of tissue are washed in running water for twenty-four hours.

Embedding: Paraffin embedding is preferred, but, where feasible, celloidin may be used. These methods are described in Mallory's book *Pathological Technique*, also in standard texts on histology or pathology.

Sectioning: Reference should be made to the above texts for this procedure. *Thin* sections (10 micra or less) are essential because examination for bacilli necessitates oil immersion microscopy. Thick sections obstruct transmission of light and make detection difficult. It is also essential that the sections be

[1] Presented to the American Trudeau Society at its annual meeting in Philadelphia, May 6, 1942.

well fixed to the slide. Egg-white or sodium silicate (water glass) is very satisfactory.

Preparation of tissue for staining: Paraffin is removed by xylol and tissues dehydrated with decreasing concentrations of alcohol to water. Celloidin does not interfere with the stain and need not be removed.

Bacillary staining: The tissue is treated just like smears of sputum or other material. Carbol-fuchsin solution with low-heat staining is recommended.

Carbol-Fuchsin Solution

Fuchsin (basic, 3 per cent in 95 per cent ethyl alcohol)	10 cc.
Phenol, 5 per cent by volume (5 cc. melted carbolic acid crystals in 95 cc. water)	100 cc.

1. Flood the slide with the carbol-fuschsin and heat gently (to steaming) for from five to eight minutes. The longer period of heating is necessary since the bacilli are well embedded in the tissue which is not as easily penetrated by the dye as are smears of suspected material.

2. Allow stain to cool and wash gently with water.

3. Decolorize with acid alcohol until the tissue is pale red.

Acid Alcohol

Hydrochloric acid (conc.)	3 cc.
Ethyl alcohol (70 per cent)	97 cc.

In order to keep the tissue on the slide it is well to wash the slide with increasing concentrations of alcohol before applying the decolorizing acid alcohol.

4. Wash in decreasing concentrations of alcohol.

5. Wash in running water. This is an important step since it removes all traces of the decolorizing agent, intensifies the redness of the stained bacilli and permits good differential staining of the tissue.

Tissue staining: In staining the tissue for differentiation, all dyes that introduce red into the tissue are to be avoided since they interfere with the detection of acid-fast bacilli. Likewise, intense staining of the tissue is not desirable since it obscures the bacilli. A simple nuclear dye such as alum haematoxylin is advisable.

Alum Haematoxylin

Haematoxylin	1 g.
Ammonium or potassium alum	20 g.
Distilled water	400 cc.
Thymol crystals (expose to air and light for ten to fifteen days for ripening)	1 g.

Varying lengths of time are required for good staining, depending upon the fixing solution used and the concentration of dye employed. Usually one-half

to one hour is necessary for Zenker-fixed tissue. Tissues fixed in formalin or alcohol can be decolorized with 1.0 per cent acetic acid, or 3.0 per cent acid alcohol, as mentioned above.

1. Wash in running water to bring out the full intensity of the haematoxylin stain in the tissue.

2. If better differential staining of the tissue is desired, almost any contrast stain may be employed, provided it does not interfere with the red stained tubercle bacilli. Orange G, methylene blue, picric acid or brilliant green give satisfactory results.

Preparation of tissue for microscopic examination: Permanent mounts are desirable. These are routinely prepared as follows:

1. Dehydrate in increasing concentrations of alcohol.[2]

2. Immerse in xylol. If tissue is allowed to remain in xylol for periods longer than one hour, destaining of the bacilli occurs.

3. Neutral balsam (one or two drops, depending upon area of tissue).

4. Cover slip (thin enough for oil immersion lens).

TUBERCULIN TESTING IN GUINEA PIGS

Tuberculin testing of guinea pigs may be done for two purposes: (*a*) to assure one that stock pigs are free of tuberculosis; (*b*) to test guinea pigs used for diagnostic purposes to ascertain whether or not the inoculum of suspected material has produced tuberculous infection. The implications of the first are simple and obvious. As to the second, it will occur to many to question the necessity of this procedure because, after all, one is seldom in such a hurry to make a diagnosis that the inoculated guinea pigs have to be tested rather than allowed to run the ordinary course for autopsy. However, in special cases this procedure may be indicated.

The test is made preferably from fourteen to twenty-one days after inoculation. A positive reaction in a previously negative guinea pig indicates almost invariably the presence of tuberculosis. Tests may be made and interpreted and the guinea pig sacrificed if it reacted to tuberculin. The most important sites for examination are the lymph nodes draining the area of infection because macroscopical tuberculosis of the viscera may not be visible at this early period. The lymph nodes are removed, sectioned grossly and smears prepared and stained for acid-fast microörganisms. In the absence of necrosis, microscopical sections of the nodes should be made and studied for tuberculous tissue or tubercle bacilli.

[2] Isopropyl alcohol has been used quite successfully for this purpose as it dehydrates well up to where absolute alcohol is needed. It is much less expensive than is ethyl alcohol and is readily available.

Procedure:

1. Two guinea pigs should be used.
2. The hair is plucked or shaved from the side of the abdomen. A white area should be selected since a tuberculin reaction is more easily seen in nonpigmented than in pigmented skin.
3. Old Tuberculin (0.1 cc. of 5 per cent) is injected intracutaneously as in clinical administration and the reaction is read twenty-four and forty-eight hours later.

Interpretation: If a tuberculin reaction results, one of the two guinea pigs must be sacrificed. A positive diagnosis can be established only if this guinea pig shows gross or microscopical evidence of inoculation tuberculosis, that is, tuberculosis of the tissues at the site of inoculation and some spread to other organs. If no tuberculosis is found, the other guinea pig should be kept for at least eight weeks.

If both guinea pigs are tuberculin-negative following inoculation, they should be kept three months before autopsy is performed or tuberculin tests may be repeated at intervals of two weeks. Complete autopsies need not be described, but reference should be made to the location of the lesions with particular emphasis on the lesion at the point of injection and the draining lymph nodes. If these are involved the animal should be reported as having "inoculation tuberculosis." In the absence of such local lesions, any visceral tuberculous involvement is most likely not caused by the injected material.

SUBJECTS UNDER STUDY

The Committee has under active study:

1: The evaluation of fluorescence microscopy.

2: The reëvaluation of the methods of reporting sputum examintions (especially Gaffky scale).

Data are not sufficient at present to justify a detailed report.

NOTICE

War Conference

The medical, surgical and industrial hygiene experts who are so ably safeguarding the well-being of more than 20 million industrial workers have agreed to pool their knowledge and exchange their experiences regarding the many new and complex problems of today's wartime production. For this purpose their organizations

The American Association of Industrial Physicians and Surgeons,
The American Industrial Hygiene Association, and
The National Conference of Governmental Hygienists

are combining their annual meetings in a four-day WAR CONFERENCE at Rochester, New York, May 24–27, 1943. Among the problems to be discussed from a practical standpoint are:

The mass entry of women into industry;

Older-age employees, with their various associated problems; proper placement and employability considerations of the 4F rejectees;

Rehabilitation and proper employment of those already discharged from the military services because of disabling conditions;

Toxic and other hazards from new substances, new processes, and the use of substitute materials;

Absenteeism; fatigue; nutrition;

Effects of long hours; double shifts; two-job workers; overtime; increased industrial accident rates;

Advances in the treatment of illnesses and injuries, and many others.

This joint meeting will be a report on the state of the nation, by the men who know, in matters of industrial health. Dr. William A. Sawyer, Medical Director of Eastman Kodak, is General Chairman; Dr. James H. Sterner and Lieut. Com. J. J. Bloomfield are arranging the programs for the industrial hygienists.

Physicians and surgeons, hygienists, engineers, nurses, executives—all who are interested in the problems of industrial health and their solution—are invited to attend as many of the sessions as they can arrange for; no registration fee is required.

"PHYSIOLOGICAL" CHANGES IN BREATH SOUNDS AND TUBERCULOSIS

The Relation between Altered Physical Findings in the Upper Lobes and a Primary Tuberculous Complex in the Lung

RICHARD T. ELLISON[1] AND J. GERSHON-COHEN[2]

It has been the teaching over many years that the observed alterations from normal in the breath sounds heard over the right apex in certain persons is physiological. It is not necessary to document this statement as reference to any standard work on physical examination, old or new (1), is sufficient. Many explanations have been offered for this alteration of physical findings, none of which have been entirely satisfactory. It has been a personal impression of one of the authors (R. T. E.), gained from over twenty years of intensive chest work, that in recent years the incidence of the so-called physiological changes in the right apex is not as great as it was, also that the incidence has always been greater among chest clinic patients than in those presenting for "health examinations."

Some six or eight years ago a correlation was observed between alterations in the physical signs in the right apex and changes in the X-ray film. The physical examinations at that time were recorded by R. T. E. and the X-ray films were reported by J. G. C., each without any knowledge of the others findings. This correlation was so striking that it suggested further study but it was not until recently that an opportunity presented itself to take up this problem again.

Further impetus to attack this problem was given by the changes that have occurred in recent years in several lines of thought bearing directly on the matter in hand. The knowledge of the anatomy and pathological physiology of the lungs has greatly increased. Of even more importance, however, is the fact that much of the tuberculous infection seen in American cities has become ephemeral in nature (2) and the ideas regarding the permanence of tuberculous allergy during the lifetime of an individual have undergone radical changes (3, 4, 5, 6, 7, 8, 9, 10).

It seemed timely, with this increased knowledge, to attempt some correlation of these new facts with the previous observation which might lead to a better appreciation of the significance of the altered physical findings in the upper zones of the lungs, especially in the upper right. If it could be shown that changes demonstrable in the upper lobes are not physiological but represent pathological physiology with impairment of function due to definite anatomical changes elsewhere, then this potential *locus minoris resistentiae* might have some bearing on the problem of the localization of tuberculous lesions in the upper lobes.

With this in mind, a study was undertaken to correlate the physical signs, the tuberculin reaction and the X-ray findings in an unselected group of persons.

[1] 1614 Locust Street, Philadelphia, Pennsylvania.
[2] 255 South 17th Street, Philadelphia, Pennsylvania.

METHOD OF PROCEDURE

Material used: The cases used in this investigation were collected in several clinics for pulmonary disease. Mostly they were children from families in which there was known pulmonary tuberculosis and for this reason it must be emphasized here that the percentage of reactors to tuberculin and the number of cases showing other evidence of tuberculosis do not represent a true picture of the incidence of these findings in the population as a whole. No cases were included which showed any evidence on X-ray examination of tuberculosis which had advanced beyond the primary phase. Cases of fresh primary complexes were included but the number of these was small and the remainder of cases showing tuberculosis represent examples of healing or healed primary complexes. No cases were included in which any other pulmonary disease could be demonstrated by either physical examination or X-ray films. The only absolute requirement for inclusion in this series was a physical examination, a tuberculin test and a chest X-ray film done within a reasonably short interval of each other.

Physical examination: All physical examinations were done by R. T. E. without any previous knowledge of the tuberculin reaction or the X-ray findings. After ascertaining that there was no gross evidence of any pathological process in the lungs, special attention was given to the upper parts of the chest.

The physical findings were recorded under the terms hypoventilation, retraction and atrophy. These findings were noted on the right and left sides, both front and back.

Hypoventilation: Under this term were noted certain changes in the breath sounds. The areas of the chest wall that were auscultated were below the clavicle in front and above the level of the scapular spine in back. Before special attention was given to these areas, however, an effort was made, by auscultating the lower and middle parts of the chest wall, to determine the type of respiratory murmur that was normal for each person.

The changes that were recorded are those alterations in the respiratory murmur that have been considered, in the past, to be normal physiological variations for these areas. These changes from the normal vesicular murmur consisted first of a harsher sounding and higher pitched inspiratory sound. Of greater significance, however, was the finding of an expiratory sound that was more definitely audible and of longer duration. Over the areas of the lung under discussion the normal expiratory sound is so faint that it is heard only during exaggerated breathing. It was felt that, with the normal respiratory murmur of the lower and lateral parts of the chest for comparison, it was possible to recognize alterations in the breath sounds on both sides in the same person. It was therefore possible to record bilateral hypoventilation.

The changes in the respiratory murmur varied greatly in intensity. It was comparatively easy to recognize the absence of any change or the definite presence of these alterations, but difficulty was experienced at times in border-line cases. The finding of changes in the respiratory murmur over the upper lobes were recorded, therefore, as 0, ±, 1, 2, 3.

Retraction: It is well known that the area of pulmonary resonance can be

followed over the apex of the lung from front to back. This band of resonance is known as Koenig's isthmus. In the present investigation the edges of this band were outlined both in front and back on each side. This was done by percussing from flatness to resonance, in front along a line from the thyroid cartilage to the apex of the axillary fold and in back along a line from the occiput to the outer end of the spine of the scapula along the ridge of the trapezius muscle. If the band of resonance was of equal width on each side it was not thought possible to say that this was either a normal condition or represented bilateral retraction and, therefore, retraction of the apex was noted only when there was a definite narrowing of one band of resonance as compared with the other. No effort was made to indicate the degree of narrowing. Retraction was therefore recorded only as 0 or +.

Atrophy: Underdevelopment or atrophy was estimated by inspection and palpation; no effort being made to distinguish between involvement of the muscles or the subcutaneous tissue alone. As in the case of the shoulder strap of resonance, it was felt that one side of the body had to be compared with the other and that, for this reason, bilateral involvement could not be recognized. In front the mass, consistency and tension of the pectoral muscles, especially the pectoralis minor, were estimated on both sides along with the amount of subcutaneous tissue. If one side was definitely smaller it was recorded as + (atrophy present) without any attempt to estimate the degree of involvement. It was found that in well marked cases there was no difficulty in recognizing a loss of volume associated with a certain stringiness of texture and an increase in tension of the muscle masses on one side as compared with the other. In back, the same differences, when present, could be recognized with even greater ease on grasping the muscle mass of the trapezius and the supraspinatus on each side.

In young females at or beyond the age of puberty the atrophy of the subcutaneous tissue extended to the developing mammary glands. The asymetry of the breasts could usually be detected by inspection but at times palpation was necessary. When asymetry was found a note was made to that effect.

Tuberculin reaction: The tuberculin reaction was determined in most instances by the Volmer patch test. In some cases Purified Protein Derivative, one or both strengths, was used. The Volmer patch test was selected chiefly because of the ease with which it can be used. It was felt that, if the minimal reaction necessary for the test to be considered positive was made small enough, the accuracy was entirely comparable to that obtained with Purified Protein Derivative.

Such a degree of accuracy was entirely satisfactory for clinical investigation. This was in agreement with an opinion expressed by Long (11).

The tuberculin reaction was considered to be positive if:

1: When using the Volmer patch, it was possible to tell where the test squares had been applied. The minimal reaction consisted of a reddish-brown discoloration of the skin limited to the size of the test squares of gauze. Inflammatory induration of the skin was not necessarily present. If this minimal reaction was found only under the test

squares and not under the control, it was felt that the reaction was due to the tuberculin. *2:* When using Purified Protein Derivative, there was an inflammatory reaction of 5 mm. or more at the site of the injection of the second strength.

In the present study no effort was made to correlate the degree of tuberculous allergy with the other findings.

X-ray films: Routine films were made in each case. These films were made in several different institutions. In this investigation only the posterio-anterior films were read, even though oblique or lateral exposures were available. Films were intrepreted by J. G. C. who did so without any previous knowledge of the results of the physical examination or the tuberculin test.

Record was made of any evidence of a present or preëxisting primary tuberculous complex. Notation was made in each case of the occurrence and location of parenchymal foci and the involvement, in one or both sides, of the regional lymph nodes.

DATA OBTAINED

The data to be presented and analyzed were obtained from the examination of 450 cases. These cases were obtained in clinics for tuberculosis and from other sources where the incidence of tuberculosis was high. They do not, therefore, represent a cross section of the general population and the occurrence of positive evidence of tuberculosis is much higher than in a more diversified group. The age distribution of the group is shown in chart 1.

As the object of the investigation was to establish the relationship, if any, between changes in the physical signs in the lungs and tuberculosis, the first thing was to analyze the data collected with this in view (table 1). In this table the physical signs were considered to be positive only when there were changes in the breath sounds. Atrophy and/or retraction occurring alone was not considered sufficient.

It is obvious that there are eight possible combinations of the three factors, physical signs, tuberculin reaction and X-ray findings. It will be convenient to consider each of these groups separately and to inquire into the possible explanations for the disagreement in the findings in each group.

Group 1: In this group there is no necessity of any explanation as all the findings are in agreement.

Group 2: The failure of the findings to agree, in this group, might be explained by assuming that the X-ray evidence might have been positive on more complete study. In this case a certain number of this group would fall into group 1. Also this group might represent cases in which there was a primary phase tuberculosis which had healed without leaving calcification or other X-ray evidence.

Group 3: This group includes those cases in which there has been complete healing of the primary phase with the disappearance of allergy but a persistence of the other two findings.

Group 4: In accounting for this grouping there are several possibilities. As in group 2 the X-ray evidence might have been positive on more complete study.

Or this group might include cases of the complete healing with the loss of allergy, of cases otherwise falling in group 2. There is also the possibility that other conditions than tuberculosis might lead to the changes in physical findings.

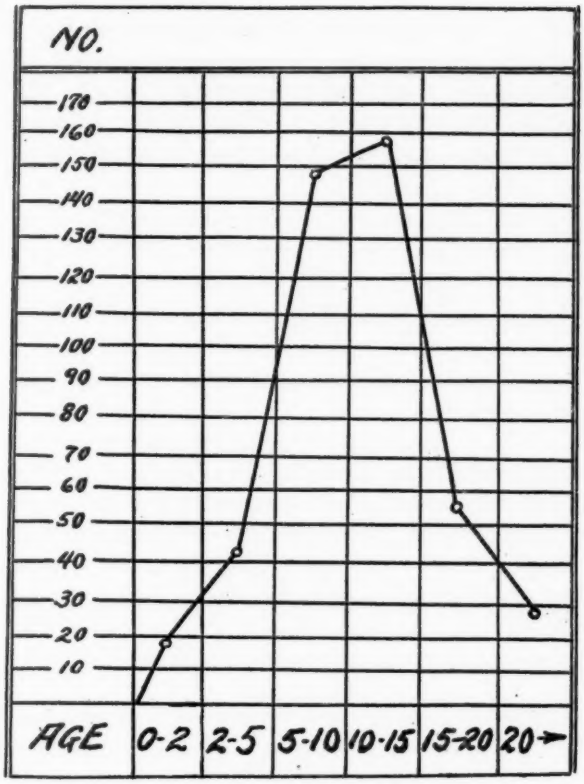

CHART 1. Age distribution of 450 cases

TABLE 1

Summary of 450 cases

GROUP	PHYSICAL SIGNS	TUBERCULIN REACTION	X-RAY	NUMBER OF CASES	GROUP	PHYSICAL SIGNS	TUBERCULIN REACTION	X-RAY	NUMBER OF CASES
1	Positive	Positive	Positive	158	5	Negative	Negative	Negative	34
2	Positive	Positive	Negative	75	6	Negative	Negative	Positive	12
3	Positive	Negative	Positive	54	7	Negative	Positive	Negative	17
4	Positive	Negative	Negative	79	8	Negative	Positive	Positive	21
				366					84

Finally the physical examination may have been in error and these cases should have fallen in the next group.

Group 5: Here as in group 1 the findings are all in agreement.

Group 6: This group might include cases in which there had been complete healing of a primary complex too small to result in altered physical findings. Or the physical examination might have been in error, thus throwing these cases into group 3.

Group 7: In this group would fall all the case of extrapulmonary primary complexes.

Group 8: In this group would be found those cases in which the primary complex was so recent that sufficient time had not elapsed for the alteration in physical signs to develop. Also the physical examination might be in error and these cases might belong in group 1.

It must be firmly kept in mind that clinical tuberculosis is never stationary but is always moving, usually very slowly, either forward or backward. It is to be expected, therefore, that, over a sufficiently long period of observation, a case will be found to pass successively through two or more of these groups. The exact pattern of the progression must be left for a future communication. Sufficient time has not elapsed, as yet, to study this point in a large enough number of children but in the few cases observed the indications are that this sequence of events may be as follows. All children start in group 5, with the onset of tuberculous infection the child then passes into group 8. After a period of time, which probably varies with the age of onset but which is measured in years, the child passes into group 1. If the infection is very slight the child may remain indefinitely in group 7 or 8, or regress to group 5 again. Once in group 1 the individual usually remains there for life but it has recently become evident that a certain number regress into group 3 or 6.

When the figures in table 1 are analyzed it is found that in 450 cases examined:

Physical signs, tuberculin reaction and X-ray agree in 44 per cent..... (Group 1 & 5)
Physical signs and tuberculin reaction agree in 62 per cent.... (Group 1 & 2, 5 & 6)
Physical signs and the X-ray findings agree in 58.5 per cent... (Group 1 & 3, 5 & 7)
Of 360 cases with positive physical signs
78 per cent have confirmatory evidence of tuberculosis..... (Group 1, 2 & 3)
64 per cent are confirmed by the tuberculin reaction..... (Group 1 & 2)
58 per cent are confirmed by the X-ray findings..... (Group 1 & 3)
43 per cent are confirmed by both tuberculin reaction and the X-ray findings..... (Group 1)
Of 337 cases with evidence of tuberculous infection..... (Group 1, 2, 3, 6, 7, 8)
85 per cent have positive physical signs..... (Group 1, 2 & 3)

We believe that, from a statistical standpoint, these figures are impressive and tend to substantiate the relationship between tuberculosis and the changes in physical signs over the upper parts of the lungs. Absolute proof of such a relationship would, of course, depend on demonstrating the absence of such changes before the tuberculous infection. This would necessitate the examination of children who had been closely followed from the age of two years or younger and were definitely known never to have previously been infected with tubercle bacilli.

If from evidence presented in table 1 it is considered established that the changes in physical signs are definitely related to tuberculous infection, the next step is a more detailed analysis of the connection between the physical signs and involvement of the hilum.

In table 2, therefore, physical signs are correlated with X-ray evidence of primary phase tuberculosis of the lungs. In this connection it was considered that the finding of a Ghon tubercle was presumptive evidence of involvement of the regional lymph nodes on that side in spite of the fact that the single postero-anterior X-ray film failed to demonstrate such involvement.

Of 366 cases showing physical signs
79 per cent showed such signs only on the right side;
21 per cent showed such signs on both sides.
Of 364 cases showing physical signs on the right (right only and bilateral)
50 per cent showed definite or presumptive (primary focus only) evidence of tuberculous involvement of regional lymph nodes on the right.
Of 285 cases showing physical signs on the right only
48 per cent showed definite or presumptive evidence by X-ray examination of involvement of the regional lymph nodes on the right.
Of 81 cases showing physical signs on the left (left and bilateral)
55 per cent showed definite or presumptive (primary focus only) evidence of tuberculous involvement of the regional lymph nodes on the left.

TABLE 2

Relation of physical signs to the pulmonary primary complex

PHYSICAL SIGNS	X-RAY EXAMINATION												TOTALS
	Primary focus only			Primary complex					Regional lymph nodes only			Negative	
				Primary focus									
				Right		Left		Bilateral					
	Right	Left	Bilateral	Regional nodes		Regional nodes			Right	Left	Bilateral		
				Right	Bilateral	Left	Bilateral						
Right	17	2		17	29	11	11	1	8	6	54	129	285
Left					1		1						2
Bilateral	5	1		3	6	2	3	2	3	4	25	25	79
													366

It is felt that, recognizing the limitations of the X-ray in the demonstration of tuberculous involvement of the hilar and tracheobronchial lymph nodes and also the incompleteness of a single postero-anterior film in the X-ray examination, the above figures are highly suggestive that tuberculous involvement of the hilar and tracheobronchial nodes bears a definite causal relationship to the abnormal physical signs.

Table 3 is an analysis of the 215 cases showing definite X-ray evidence of

tuberculous involvement of the regional lymph nodes of the lung. It is from such an analysis that the most convincing evidence should be obtained, for if there is any connection between alteration in physical signs and involvement of the regional lymph nodes it should show here.

Of 215 cases with definite X-ray evidence of regional lymph node involvement
85 per cent have positive physical signs or definite alteration in physical findings.
Physical signs are three and one-half times as frequent if the tuberculin reaction is possitive (142 to 42).
Bilateral involvement of the regional lymph nodes was three and one-half times as frequent as unilateral involvement (154 to 61).
Of 161 cases with definite involvement of the right regional lymph nodes (right only and bilateral)
85 per cent had altered physical signs on the right.
Of 179 cases with definite involvement of the left regional lymph nodes (left only and bilateral)
23 per cent had altered physical signs on the left.

TABLE 3

Analysis of cases showing regional lymph node involvement

REGIONAL LYMPH NODE INVOLVEMENT	PHYSICAL SIGNS								TOTALS
	Tuberculin-positive				Tuberculin negative				
	Negative	Right	Left	Bilateral	Negative	Right	Left	Bilateral	
Right	2	19	1	4		9		1	36
Left	3	12		5	1	4			25
Bilateral	15	75	1	25	10	19		9	154
									215

The fact that 86 per cent of cases with lymph node involvement show alteration of physical signs undoubtedly is more than coincidence and definitely establishes a causal relationship between the two findings.

This table also shows that, in those cases in which the primary tuberculous infection is so completely healed that the tuberculin reaction fades out, the incidence of altered physical signs is only one-third that of cases in which the healing is incomplete, and a positive tuberculin reaction persists. In other words, the more severe the infection the more permanent are the changes in physical signs.

This table supports the belief that, no matter on which side the primary focus occurs, the lymph nodes throughout the entire mediastinum are usually involved.

It also demonstrates clearly that physical signs are produced more easily on the right than on the left by involvement of the regional lymph nodes on the corresponding side. With an almost identical number of cases of involvement of the right and left regional lymph nodes, alteration in physical signs was four times as frequent on the right as on the left.

DISCUSSION

A consideration of the data presented above can lead to only one conclusion: that a definite relationship exists between involvement of the hilar and tracheobronchial lymph nodes by tuberculosis and changes in the physical findings over the upper part of the chest. These changes include the so-called physiological alteration in the breath sounds, retraction of the apex and asymetry of the musculature and subcutaneous tissue of the two sides. Complete agreement between the various findings cannot be expected because the figures are based on two phases of "the art and practice of medicine" in which the value of the interpretation is due entirely to personal knowledge and experience. Also the interpretation is not as simple as the separation of black from white because many border-line cases have to be considered.

It is our firm belief, however, that this intimate relationship is one of cause and effect, that tuberculous involvement of the hilar and tracheobronchial lymph nodes leads to the observed changes in the physical findings. If this is so, some explanation must be offered. While the full development of the thesis cannot be presented at this time the main points can be outlined.

Macklin (12, 13) has shown that for the proper functioning of the upper posterior parts of the lung the hilum must move downward and forward during inspiration. Conversely if the hilum is fixed there is impaired function of the pulmonary parenchyma in the supero-retro-hilar region.

For a diagrammatic presentation of the normal function and the results of hilar fixation shown for the three planes through the lung, the reader is referred to figures 2, 3, 4, 5, 6, 7 in Macklin's article (13).

Macklin says, "It will be evident that an increase in the amount and density of the connective tissue of the root and its extentions, particularly if accompanied by adhesions to the posterior thoracic wall, could have no other than an inhibiting effect on normal bronchial movements. Such a condition might well diminish, or eliminate, the normal elongation and retraction of the bronchial stems, and might even overstep the root region proper and be prolonged into the bronchial tree itself." And, again "lymphadenitis and lymphangitis of the root region, of tuberculous or nontuberculous etiology, might well cause movement restriction, in the acute or chronic stages."

There can be no argument that primary phase tuberculosis is the commonest cause of inflammatory reaction in the hilar and tracheobronchial lymph nodes. Nor that a periglandular inflammatory reaction, matting the nodes together, is characteristic of tuberculous adenitis. Such a periglandular reaction undoubtedly produces "an increase in the amount and density of the connective tissue of the root."

If then, the root becomes fixed as a result of the tuberculous adenitis there must be impaired function. Macklin says, "if the root be stiff and fixed in position, one can hardly conceive of the territory lying behind and above it being properly ventilated." The result of fixation of the hilum, then, would be hypoventilation of parts of the upper lobe. This hypoventilation we believe is the cause of the changes in breath sounds in the upper parts of the lung.

If the root is fixed and there is hypofunction above and behind it, there develops in time a loss of volume of that part of the lung. This loss of volume readily accounts for the retraction of the apex.

The explanation of the connection between underdevelopment of the muscles and subcutaneous tissues of the chest wall and fixation of the hilum is based on the following. First, the hypofunction of the parts of the lung lying above the hilum results in the atrophy of disuse or hypoplasia of the bronchial walls. This has been suggested by Macklin who says, "The effect of prolonged restrain on normal function of the S. R. R. region could hardly be other than adverse. The bronchi, denied their usual freedom of movement, would probably become atrophic." Next Pottenger (14, 15) has written extensively on the existence and effects of viscerosomatic reflexes. For the lung he has shown that disease processes in that organ cause trophic changes in the muscles and subcutaneous tissue of the chest wall on the corresponding side. It is our conception, however, that actual inflammation is not necessary to initiate this reflex but that it can be stimulated by the atrophy of the bronchi and interstitial tissue, resulting from hypoventilation.

CONCLUSIONS

From the evidence presented it is felt that the following conclusions are warranted.

1. The so-called physiological alterations in breath sounds over the upper lobes are not chance findings but are the direct result of tuberculous involvement of the hilar and tracheobronchial lymph nodes as part of a primary complex.
2. In most instances the changes in breath sounds are associated with retraction of the apex of the lung and underdevelopment of the muscles and subcutaneous tissue of the upper chest wall on the same side.

CONCLUSIONES

Tomando los datos presentados, considéranse justificadas las siguientes conclusiones:

1. Las llamadas alteraciones fisiológicas en los ruidos respiratorios sobre los lóbulos superiores, no constituyen hallazgos accidentales, sino que son consecuencia directa de la invasión tuberculosa de los ganglios linfáticos hiliares y tráqueobronquiales como parte de un complejo primario.
2. En la mayor parte de los casos las alteraciones de los ruidos respiratorios se asocian con la retracción del vértice pulmonar y el hipodesarrollo de los músculos y tejidos subcutáneos de la pared de la porción superior del tórax del mismo lado.

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TUBERCULOSIS IN MENTALLY ILL PATIENTS[1]

The Problems and Difficulties of Its Treatment

ALEKSEI A. LEONIDOFF

A growing interest and increased effort to correct the high prevalence of tuberculosis (1) in hospitals for the mentally ill has been intensified for the past three or four years. In the Hudson River State Hospital at Poughkeepsie, New York, we started our search for tuberculosis among the patients in 1930, but the real planned survey came into being in 1936 (2). The first step in our plan was to give Mantoux tests with PPD and also the Vollmer patch test[2] to all patients, with the idea of comparing the two methods. We thought that by dividing the patients into positive and negative tuberculin groups, the further search for tuberculous patients would be facilitated. Table 1 will show the result of this method. At the time these tests were made tuberculin was still in common usage, though its value was later found to have been greatly overestimated. It is now generally conceded that tuberculin tests are of little value in adults and my findings bear out this conclusion.

As to the comparison of the PPD and the Vollmer method, we found but little difference between the two, the results being identical in practically every case. Moreover, both methods were unsuccessful with some of our patients. At first we thought (2) that the Vollmer patch test would be easier to give to our type of patient, but the patch was removed by 1,221 of the 7,466 patients to whom it was applied. Some of the patches were hidden and a few eaten. As for the Mantoux tests, 527 of the 7,466 patients on whom we tried to apply this test were uncooperative, a few refused the injections, while others scratched or licked the site of injection, thus nullifying the reading of the test.

We were not able to find any constant relation between X-ray findings and reactors and nonreactors, for there were positive and negative X-ray films in both groups, and the percentages were not comparable. This experience seems to be in agreement with that of other workers (3).

A number of physicians (4, 5, 6, 7) advise the use of fluoroscopy for detecting pulmonary tuberculosis. Our experience with this method since 1934 in the Hudson River State Hospital has convinced us that for the mentally ill it is most unsatisfactory: first, because there are not enough psychiatrists who are trained in tuberculosis work and roentgenology; second, because fluoroscopy takes a great deal of time and frequent and prolonged exposure to X-ray is a danger to the health of the examining physician; third, because the uncoöperativeness of the patients makes the method impracticable. Finally, and most important, a little over 5 per cent of pulmonary tuberculosis will be overlooked by this method. During my work in the Hudson River State Hospital, I have had to train three

[1] From the Hudson River State Hospital, Poughkeepsie, New York.

[2] The material for these tests was made available through the generosity of the Lederle Laboratories, Pearl River, New York.

different physicians, only to have them transferred after acquiring some knowledge of fluoroscopy and tuberculosis. We now use fluoroscopy principally before and after pneumothorax treatments.

I have previously (8) stressed the point that the usual physical examination of the chest for pulmonary tuberculosis is extremely difficult, and our experience has led us to conclude that this method can be supplied with good results in only a very small percentage. On the physical examination reports in the Tuberculosis Service, such notations as these are most frequent: "patient is uncoöperative;" "patient is very talkative and makes examination impossible;" "patient is deteriorated and does not respond to questioning;" "patient refuses to breathe or cough as requested;" "patient is resistive;" and many other similar explanations mark the futility of effort in this direction. In many cases the past history or history of present illness, could not be elicited; in others the version was so garbled that its value became questionable. Loss of weight could not be used as a guide, because psychic disturbances enter into the equation. The sedimentation test was tried on many hundreds, but in many cases it did not give the information when most needed, that is just before spread or

TABLE 1

Number of patients in survey

	POSITIVE	NEGATIVE	UNCOÖPERATIVE	TOTAL NUMBER
Mantoux tests	4,958	1,981	527	7,466
Vollmer patch	4,563	1,682	1,221	7,466
Employees in survey				1,066

early infiltration. Our experience is in agreement with that of Klemm (9) who found, "a normal or prolonged sedimentation rate in 53 cases of active pulmonary tuberculosis with positive bacteriologic and roentgenologic findings." Even the pulse rate and temperature charts present confusing data on account of the involvement of the sympathetic or vagus systems.

Abandoning all the methods mentioned above, we began a survey with roentgenography. It is generally conceded that "mass radiography will assist in controlling the spread of tuberculosis" (10). In an effort to avoid repetition or omission of examination, the survey was started according to buildings, but for all our good intentions, our survey was frequently disarranged. Only a physician working in an institution for the mentally ill can appreciate the difficulty of such a task. The overcrowding and constant transfer of numerous patients to and from other institutions, as well as the difficulties which arise from the understaffing of personnel, kept our work endlessly confused. At times lack of X-ray films, which could not be purchased ahead of time because of the budget, accidental breakage of the X-ray machine and illness of the technician added to our burdens.

By January, 1942 the survey was practically finished, and 752 of the 7,466

patients had been isolated and diagnosed.[3] Of this number, 163 were under observation, of whom 77 proved to be negative. This left a total of 675, or 8.8 per cent incidence of clinically significant tuberculosis in this institution. During this time we X-rayed 1,066 employees and found 30 with tuberculosis, giving 2.8 per cent. Twenty-seven employees out of the group definitely contracted tuberculosis while in line of duty and since the passage of the Compensation Law in September, 1935, 16 employees have received compensation. Incidentally, 2 out of the group were working in the laundry, one was assistant chef and one was a dietitian. Taking into account the trying conditions under which the employees work, we consider it very fortunate that only 3 have contracted tuberculosis in the unit. The precautions listed below may be considered as largely responsible for our good record:

1: We reëxamine all employees every four months and more frequently if needed.
2: We try to dissuade persons of the younger group against work in the Tuberculosis Service.
3: All prophylactic measures are enforced, such as the wearing of gowns and masks and personal hygiene.
4: Frequent formal and informal talks are given, stressing the danger of tuberculosis and its tragic consequences.
5: Attendants are urged to rest if suffering from slight colds or other ailments. In this way the spread of disease among patients is reduced and the employees protected during periods of lowered resistance.

The number of single films used for the combined number, about 9,500, made the survey quite expensive. An extra thousand films were taken for recheck of the 163 patients under observation and the replacing of films spoiled by uncoöperative patients.

But our work was not ended with the single survey, for 13 patients who had been previously negative became positive. Wicks (11) and Plunkett *et al.* (12) report similar occurrences in their extensive resurveys. As the single survey gives only a false sense of security, we plan to make another survey soon, using the miniature X-ray film which has come into usage lately and has proved of tremendous value (13, 14, 15, 16, 17). Its low cost, small space required for storing films and, most important, the speed with which it can be applied makes it most desirable for institutions for the mentally ill. The Division of Tuberculosis and Mental Hygiene of the New York State Department of Health has drawn up a plan (12) for the control of tuberculosis in all mental hospitals by means of the miniature X-ray (4 x 5) films. They already have two mobile units with trained personnel which are being sent from one institution to another, and we hope they will come to the Hudson River State Hospital to conduct reëxaminations. It is expected that more new cases will be found and, in the future, it probably will require similar examinations almost every two years. In fact, I believe that every institution the size of the Hudson River State Hos-

[3] The number of patients reported last year (8), 4,800, was taken from the survey made by the unit, whereas the number presented here, 7,466, includes those who have been X-rayed by the main X-ray Department.

pital should purchase such an apparatus, because the number of chest films ordered by the ward physicians is quite high. Besides these, the number of new admissions and discharges averages about 1,300 per year, and the paroled cases between 350 and 400, and all of these have to be X-rayed. The equipment will pay for itself within a short time.

We agree with the workers (18) who advocate that all patients who have been subjected to shock therapy be reëxamined and re-X-rayed at frequent intervals. In our survey, we have already found 6 tuberculous patients out of 354 so treated.

The collection of sputum presents another problem, for there is always a great number of uncoöperative patients from whom specimens could not be obtained. However, out of 453 patients, 193 had positive sputum. We now have in the unit our own laboratory with a capable technician who has begun to replace the smear method with the concentrated method and gastric lavage, and certainly more positive sputum cases will be discovered by these means. In questionable cases we use guinea pig inoculations.

Since December, 1934, we have had 453 patients in our tuberculosis buildings whom we have tried to treat in a manner similar to that used in sanatoria for mentally normal patients but, here again, we have encountered almost insurmountable obstacles. Normal persons realize that the procedures of sanatorium treatment, such as bed-rest, mental and physical relaxation, control of cough and compliance with rules and regulations, are devised for their own welfare. To the mentally ill, our buildings are nothing but places of detention and the rules and regulations are meaningless. Therefore it is evident that the expected coöperation and desired friendly relationship between the patient and physician are lacking.

There is a decided difference of opinion among writers as to treatment; in several instances, the results reported are contradictory. For example, it has been claimed that "the treatment of the tubercular psychotic patients differs in no way from the mentally normal," (19) and "little difficulty has been encountered in giving pneumothorax treatments to any of these patients. One hundred have been given pneumothorax, and in only one case have treatments been discontinued because of the patient's refusal to coöperate" (4). In our series (8), the result was quite the opposite: 72.71 per cent were ineffective, 42.4 per cent of whom were dead at the end of the first year. It is our conclusion that pneumothorax treatment is not suitable for the mentally ill patient.

The following information has been gathered over a period of six years on patients who have been under sanatorium treatment:

1: Dementia praecox has been the largest group, 66.4 per cent of the tuberculous patients; manic depressive, 10.2 per cent; psychosis with general arteriosclerosis, 3.8 per cent; psychosis with mental deficiency, 2.4 per cent; and the rest were variously distributed under other psychiatric diagnostic nomenclature.

2: The majority of patients were diagnosed as tuberculous after being in the institution for from five to fifteen years.

3: The group between the ages of thirty and sixty are most frequently afflicted. In patients over seventy years of age, there were 7 patients with far advanced and 9 with

moderately advanced pulmonary tuberculosis who have been in the institution many years and have been treated for emphysema, chronic bronchitis, asthma and other conditions.

4: During that time we have had only 2 cases of tuberculous meningitis, and the course of illness differed in no way from that of mentally normal patients. Tuberculous enterocolitis, epididymitis and laryngitis are the same in course and frequency, although one would expect more cases in the latter group since usage of loud voice is a common occurence in the mentally ill.

5: We also noted that patients who are more or less coöperative frequently do much better than those who are uncoöperative. However it is hard to draw the line between coöperative and uncoöperative, because one day the coöperative patient becomes uncoöperative and vice versa.

TABLE 2

End-results of sanatorium treatment (excluding pneumothorax)

56 per cent poor results out of 399 patients

YEARS	NOT IMPROVING								DEAD								OTHER SANATORIA AND HOME							
	Minimal		Moderately advanced		Far advanced		Total		Minimal		Moderately advanced		Far advanced		Total		Minimal		Moderately advanced		Far advanced		Total	
	C*	U**	C	U	C	U	C	U	C	U	C	U	C	U	C	U	C	U	C	U	C	U	C	U
Under 1 year	4	4	2	1	2	2	8	7	2	4	8	18	22	33	32	55	2	2	2	1	4	1	8	4
1–2 years	8	12	6		2	1	16	13	1	5	7	6	1		9	11		1			1		1	1
2–3 years	5	10	1	1	3		9	11	3		1			1	4	1			1				1	
3–4 years		2	4	6	1		5	8	2	3					2	3								
4–5 years		2	1	1	1		2	3		1	2	1			2	2								
5 years and over		1	1				1	1		2	2				2	2								
Total.....	17	31	15	9	9	3	41	43	8	15	20	25	23	34	51	74	2	3	3	1	5	1	10	5

* C—Coöperative.

** U—Uncoöperative.

Tables 2 and 3 demonstrate the end-result of sanatorium treatment, excluding pneumothorax cases. Out of 399 patients, 44 per cent showed definite improvement, whereas 56 per cent were in the poor group with 31.3 per cent dead; more than half of those died within one year. One can readily see that the number of patients with minimal tuberculosis in the poor group is extraordinarily high. The great majority of cases of the exudative type had been in this group, and rapid spread of involvement had been the usual sequence.

Table 4 (20) certainly gives the impression that one might be justified in concluding that a pneumothorax is contraindicated in psychotic patients. A final decision cannot be made, however, until a larger number of cases is studied, but it has been our experience that those cases in which the mental condition even approximates a coöperative normal are few and far between. We feel that this factor is the chief cause of our difficulties.

Eighteen patients were readmitted to the tuberculosis unit, 10 within one year,

3 after two years, one after three years and one after four years. At the beginning we thought we would recheck the apparently arrested once a year and the quiescent group once every three months, but, when we had to readmit more than half within one year, we decided to recheck our patients more frequently. In other words, the accepted procedure for follow-up in sanatoria for normal persons is not applicable to mentally ill patients, for they should be kept under close observation and examined more frequently. In fact, we should not discharge quiescent patients, but unfortunately we have had to return some of them to their respective services when they become disturbed, because we have not the facilities for caring for them in our unit. The ideal arrangement would be to keep all tuberculous patients in separate buildings for an indefinite period.

TABLE 3

End-results of sanatorium treatment (excluding pneumothorax)

44 per cent good results out of 399 patients

YEARS	APPARENTLY ARRESTED								QUIESCENT								IMPROVING							
	Minimal		Moderately advanced		Far advanced		Total		Minimal		Moderately advanced		Far advanced		Total		Minimal		Moderately advanced		Far advanced		Total	
	C*	U**	C	U	C	U	C	U	C	U	C	U	C	U	C	U	C	U	C	U	C	U	C	U
Under 1 year	14	2	2	2			16	4	5		1			1	6	1	13	6	1	1			14	7
1–2 years	13	18	3	2			16	20	1	3					1	3	12	4	2	2			14	6
2–3 years	6	9	1	3			7	12	4	2					4	2	6	13	1	1	1		8	14
3–4 years	2		1	1	1	2	4	3										1	1	1			1	2
4–5 years	3	3					3	3		1						1								
5 years and over	2						2										1						1	
Total.....	40	32	7	8	1	2	48	42	10	6	1			1	11	7	32	24	5	5	1		38	29

* C—Coöperative.

** U—Uncoöperative.

During the year 1941, we selected 8 cases for pneumothorax treatments, but had to abandon 6 on account of spread. The treatment failed on the remaining 2 owing to lack of free pleural space.

Our thoracoplasty group of the same year was not very encouraging either; out of 4 patients, 2 died; though the remaining 2 showed fair results. We selected 4 more for thoracoplasty, but permission for the operation was refused.

In spite of the fact that 12, our total number of thoracoplasties for the past few years, have not been very successful, I still believe that if the operations were performed by an experienced thoracic surgeon, and as early as possible, the results would be different. Of course, there will have to be many more operations before conclusions can be drawn, but I am willing to make the prophesy that pneumothorax treatments will be replaced, in the majority of cases, by selective thoracoplasty in every sanatorium. The fact is that the percentage of good results is very much higher for thoracoplasty than for pneumothorax according to the latest reports (21).

Why are the end-results of pneumothorax and sanatorium treatment of mentally ill patients so decidedly poor in comparison with those of sanatoria for mentally normal persons? We have tried in every way possible to give the patients the accepted routine, but spread of the disease indicates that something else is responsible for the failures.

Can it be food? A comparative study was made of the food allowance in a state hospital with that of a county institution and, though there is a definite increase of food rations in the latter, vitamin requirements being equal, still that does not answer our question, for quite a few of the more coöperative patients gain weight on their daily rations. The weight of the uncoöperative patient who refused to eat could not be a gauge of the rations.

TABLE 4

Comparison of results in percentages obtained at Michigan State Sanatorium (20) with those of Hudson River State Hospital

	NUMBER OF PATIENTS	STAGE OF TUBERCULOSIS AT ADMISSION			USE OF COLLAPSE THERAPY	RESULTS				
		Minimal	Moderately advanced	Far advanced		Arrested or apparently arrested	Quiescent	Improved	Unimproved or worse	Dead
Patients not treated by collapse therapy:										
Michigan State Sanatorium.....	228	22.4	21.0	56.6	0.0	25.9	8.7	4.4	35.1	25.9
Hudson River State Hospital.....	399	55.14	24.81	20.05	0.0	22.55	4.51	16.8	24.81	31.33
Combined collapse and no collapse therapy:										
Michigan State Sanatorium.....	637	9.1	34.5	56.4	84.3	57.8	15.5	4.2	7.9	14.6
Hudson River State Hospital.....	453	49.9	28.9	21.2	11.92	20.09	3.97	15.9	24.72	35.32

At first it was thought that mental and physical overactivity might be responsible for the poor results, as most of our patients are overactive, but the results were no better with the schizophrenics, particularly the catatonic group which is characteristically indifferent and underactive.

Has the confinement of hospital life, the lack of will to live and inadequate muscular activity lowered the general resistance? Frankly, I have no explanation for the poor response to treatment.

Very frequently I wonder what right I have as an internist to assume charge of patients whose mental condition is beyond my understanding. What is the solution? Would it not be better for the mentally ill patients, if psychiatrists studied tuberculosis and applied their combined knowledge in the treatment of

tuberculosis among the mentally ill? But here again arises another problem. The psychiatrist, who is assigned to tuberculosis work in the mentally ill, would have little time for the psychiatric and neurological studies upon which examinations and advancement in the department are based. It is therefore only natural that a psychiatrist would not wish to devote all his energies to the tuberculosis service. If, on the other hand, the Department of Mental Hygiene would recognize tuberculosis as a major study and make it equal to pathology, for instance, more men in state hospitals for the mentally ill might be induced to make it their final specialty without jeopardizing their chances of succeeding to higher positions. If this can be done, the problem of tuberculosis in the mentally ill will be in proper hands and I feel certain the results achieved will be much better than those presented here.

CONCLUSIONS

1. The best method of surveying the incidence of tuberculosis in institutions for the mentally ill is roentgenography.
2. A single survey is not sufficient for controlling tuberculosis in such institutions.
3. Difficulties encountered in surveying and treating tuberculous patients are stressed and discussed.
4. Apparatus for 4 x 5″ films is strongly recommended.
5. Certain rules are advised to eliminate reinfection of employees working in tuberculosis units.
6. It is again emphasized that pneumothorax treatment is not a suitable method in the mentally ill.
7. Follow-up procedure is discussed.
8. Early diagnosis and thoracoplasty are apparently the best and most promising methods of combating the spread of tuberculosis.
9. No satisfactory explanation was found for the poor results.
10. Majoring in tuberculosis by psychiatrists is recommended.

CONCLUSIONES

1. El mejor método para estudiar la frecuencia de la tuberculosis en las instituciones dedicadas a los enfermos mentales, es la roentgenografía.
2. No basta un solo estudio para el fin mencionado en dichas instituciones.
3. Señálanse y analízanse las dificultades encontradas para descubrir y tratar a los tuberculosos.
4. Recomiéndanse ardientemente los aparatos que utilizan películas de 10 x $12\frac{1}{2}$ cm.
5. Recomiéndanse ciertas reglas para eliminar la reinfección de los empleados que trabajan en unidades tuberculosas.
6. Recálcase de nuevo que el neumotórax terapéutico no constituye un método apropiado para los enfermos mentales.
7. Discútense los métodos de observación subsecuente.
8. El diagnóstico temprano y la toracoplastia constituyen aparentemente los

métodos mejores y que más prometen para combatir la propagación de la tuberculosis.

9. No se descubrió ninguna explicación satisfactoria de los malos resultados obtenidos.

10. Recomiéndase que los psiquiatras se especialicen en tuberculosis.

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INJECTION OF PROCAINE FOR PLEURAL PAIN[1]

JASON E. FARBER

In 1939 Schnur (1) reported a method for the relief of pleural pain by the injection of procaine into the chest wall. Schnur injected 32 patients who had pleural pain secondary to pneumococcus pneumonia. There was immediate relief in all cases, although 6 complained of residual soreness. Seven of the group had a recurrence of the pain within several minutes to several hours. In the remainder of the group not only was there relief of pleural pain following the injection but secondary beneficial effects were noted. There was a restoration of the rapid shallow respirations to normal, cough was facilitated and the patients were able to relax and obtain rest. Schnur infiltrated the site of maximum pain in the chest wall with 5 to 10 cc. of 2 per cent procaine, intracutaneously, subcutaneously and into the region of the pleura. Most of the procaine was injected deeply. An ordinary hypodermic needle was used for the superficial injection and a No. 19 Wassermann type needle was used for the deep injection.

We have used this method with certain modifications, for the relief of pleural pain in our tuberculous patients. The gratifying results obtained seem to justify the use of the procedure.

Fifty-two patients with pleural pain have received a total of 98 injections (table 1). Definite and immediate relief was experienced from roughly 95 per cent of the injections. Approximately 20 per cent of those injected experienced relief for only two to four hours. However, the pain was usually of less intensity when it returned. The remainder of the patients were relieved for more than four hours. More than one-half of this group had relief for twenty to twenty-four hours or longer.

POTENTIATION BY EPINEPHRINE

The first group of patients were injected with a 2 per cent procaine hydrochloride solution. The second group of patients were injected with a 2 per cent solution of procaine to which epinephrine was added. The duration of relief from pain was roughly twice as long in the second group. We have since added epinephrine to the procaine used for injection. One cc. of 1:1,000 epinephrine hydrochloride is added to each 25 cc. of procaine solution making a concentration of 1:25,000 of the epinephrine. It is well known that epinephrine causes local vasoconstriction, hence slowing up absorption and prolonging the action of procaine (2). By virtue of the slower absorption of the procaine, toxic reactions were fewer and less severe than in the first group.

PROCAINE REACTIONS

In the beginning we used approximately 15 cc. of 2 per cent procaine solution without epinephrine. Almost every patient experienced a toxic reaction, usually

[1] From the Edward J. Meyer Memorial Hospital and the University of Buffalo School of Medicine, Buffalo, New York.

mild but occasionally more severe and characterized by anxiety, restlessness and sometimes mental excitement and confusion. Whereas these reactions were fewer and less severe when epinephrine was added to the procaine, they still occasionally occurred. It was also observed that there were more nervous reactions to the procaine in the sicker patients, especially in those who were febrile. Because of these untoward reactions, chiefly overstimulation of the central nervous system, it was felt that preliminary medication with the barbiturates was essential.

PRELIMINARY BARBITURATE SEDATION

Following the use of one of the barbital compounds preliminary to the injection of procaine no severe toxic reactions have been encountered. The patient is given a hypodermic injection of 1 grain (.065 g.) of sodium phenobarbital shortly before the injection of procaine. If the barbiturate is given orally, ample time should be allowed for its action to take place before injecting

TABLE 1

Injection of varying strengths of procaine

GROUP	NUMBER OF INJECTIONS	PROCAINE	EPINEPHRINE	TOXIC REACTIONS	RELIEF FROM PAIN	PER CENT RELIEVED
		per cent				
1	20	2	0	Numerous*	19	95
2	26	2	1:25,000	Occasional	25	96
3	8	0.5	1:25,000	None	7	88
4	44	1	1:25,000	None	42	95

* Preliminary barbiturate not used.

the procaine. The barbiturates apparently prevent or counteract the toxic effects of procaine on the central nervous system (3).

Varying strengths and amounts of procaine were then used, ranging from 5 to 20 cc. of 0.5 to 2 per cent procaine. It was found that 10 cc. of a 1 per cent solution of procaine is the most suitable. There were no toxic reactions when using the 1 per cent solution. Moreover, the pain was relieved just as completely with 1 per cent as with 2 per cent procaine. The results were not as successful with the 0.5 per cent procaine as with the 1 or 2 per cent solutions, so that only a few patients were injected with it.

TECHNIQUE OF INJECTION

Whereas the majority of patients complained of pain over a fairly large area of the chest it was possible by firm palpation with the end of one finger to find a small area which was most tender and painful. This was the site selected for injection. In a few instances two painful areas were injected. A long, 22 gauge hypodermic needle is used. The hands are scrubbed, rubber gloves are worn and the usual sterile precautions observed. The skin is cleaned with iodine and alcohol and draped with a small pneumothorax sheet. A wheal is

raised in the skin, with the procaine-epinephrine solution, at the point of maximum tenderness. The needle is then projected into the subcutaneous tissue and chest wall where approximately 5 cc. is injected. Care is taken so that the needle is not in a blood vessel as the procaine is being injected. The area is well infiltrated by withdrawing the needle to the skin and inserting it in several directions. Then the needle is slowly projected to the pleura injecting the procaine as the needle moves forward. The parietal pleura is well infiltrated. Usually at this point some of the procaine inadvertently slides into the pleural space. Altogether about 10 cc. of 1 per cent procaine solution is used.

DISCUSSION

The majority of tuberculous patients with pleural pain do not need an injection of procaine. Small doses of codeine usually serve to allay the discomfort. There are, however, a number of patients whose pleural pain is quite severe and for whom the usual remedies are inadequate. It is this group which benefits from an injection of procaine. In the hands of a physician experienced in pneumothorax therapy the procedure is not only simple but quite safe. Preliminary barbiturate medication is essential for the prevention of toxic nervous reactions. The action of procaine is prolonged by the addition of epinephrine. The usual precautions which prevent spontaneous pneumothorax and pleural infection must be taken (4).

SUMMARY

The injection of procaine for the relief of severe pleural pain in tuberculous patients has proven to be a valuable treatment. The technique consists of preliminary barbiturate sedation followed by the injection of approximately 10 cc. of a solution of 1 per cent procaine with 1:25,000 epinephrine hydrochloride into the skin, chest wall and parietal pleura.

SUMARIO

La inyección de procaína para el alivio del dolor pleural intenso en los tuberculosos ha demostrado su utilidad terapéutica. La técnica consiste en obtener la sedación preliminar con barbituratos, seguida de la inyección de unos 10 cc. de solución de procaína al 1 por ciento, con clorhidrato de epinefrina al 1:25,000 en la piel, pared torácica y pleura parietal.

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THE ROUND PULMONARY TUBERCULOUS FOCUS[1,2]

I. D. BOBROWITZ

In the development of the various lung lesions of tuberculosis, attention has been called to round infiltrates. These have also been described as round foci, solitary foci or circular lesions.

This study of the tuberculous round pulmonary focus includes a series of 55 patients, 30 males and 25 females, with 47 white and 8 colored. The ages of the patients varied from fifteen to fifty-seven with 80 per cent between twenty and forty.

These cases were reviewed by examination of the X-ray films and clinical abstracts prior to admission to the Sanatorium, the Sanatorium record and the films and clinical summary furnished by the hospital, clinic, or physician providing post-sanatorium care.

The round foci could be classified as follows:

I. *Found Completely Formed:*
  Group A: Present when first seen.
  Group B: Appeared on subsequent examination.
    Subgroup 1—In area of normal lung.
    Subgroup 2—In area of infiltration.

II. *Formation Observed:*
  Group C: Resulting from the spontaneous closure of a pulmonary tuberculous cavity.
  Group D: Produced by closure of a pulmonary cavity by artificial pneumothorax.

Group A: This was the largest group with 33 cases. Single foci are usual and were present in 27 patients. Four cases had multiple unilateral lesions, (3 with two foci, and one with three). Only 2 patients showed bilateral lesions (an instance of one focus on each side and one with two foci in both lungs).

Characteristically, the focus is in the infraclavicular region and within the area of the first anterior intercostal space. In only 4 instances was the apex the site of the lesion and just as rare was the occurrence in the third interspace. However, in about one-quarter of the group, the second anterior interspace was the location of the focus. No basal lesions were observed.

The round focus did not show great variations in size and the usual diameter was 2.5 cm., with an occasional one slightly larger and a good number a little smaller.

These round lesions which are already formed when first seen are characteristically circular in outline, well defined and homogeneously dense, though some are more fibrotic than others with an occasional one even fibro-calcific. It is an isolated lesion with about 70 per cent exhibiting no surrounding infiltration,

[1] From the Municipal Sanatorium, Otisville, New York (one of the institutions of the Department of Hospitals of the City of New York).

[2] Presented at a meeting of the Otisville Clinical Society, July 11, 1942.

but a fifth of these cases showed a few fine nodules or a very small coalescent spot in the same lung, usually in the apical part of the lobe. The rest of the patients had infiltration in the form of one or a few fine nodules or a small mottled area in the vicinity of the round focus and bilateral tuberculous infiltration was not common and always of very minimal extent.

All of the round foci have similar characteristics of behavior, but in cases with multiple and bilateral lesions the individual foci showed variations. In almost half of the cases the lesions showed no changes during the observation period. In about one-third, a slight decrease in size occurred, though occasionally a slight enlargement may have preceded the diminution. As the contraction ensued, the round focus became more dense and well defined in outline and invariably retained its circular appearance. Occasionally it altered its shape, becoming oval or triangular, or rarely there would be a small band or spur-like projection from the main body. In 2 cases the decrease in size was of marked degree and the round foci were almost entirely absorbed.

Slight enlargement of the foci occurred twice (6 per cent), and in 3 patients (9 per cent) progression or cavitation took place. Two of these showed a moderate increase and the third, a considerable enlargement to a width of 3.5 cm., more than twice the diameter of the original lesion. This latter patient left the Sanatorium against advice and the final examination showed the enlarged focus with an area of clearing suspicious of cavitation. Definite cavitation of the round focus and a spread of tuberculosis throughout the lobe wherein the focus was present and the first appearance of a positive sputum characterized the 2 patients that were observed. Remarkable resolution occurred in one patient and the cavity spontaneously closed and formed a round focus again, almost identical in appearance to the original lesion. The round foci had been stable for seven, eleven and twelve months respectively in these patients before the cavitation and progression occurred.

As most of these cases showed a stability of the foci, it was not surprising to find that almost 70 per cent had a negative sputum during their sanatorium observation. However, 15 per cent of these had a history of positive reports at the onset of their illness. Positive sputa appeared for the first time in the 2 patients mentioned above who evidenced a spread of their tuberculosis. About one-third of the group could be equally divided into those with only one or two positive sputum cultures and those with occasional positive sputa. It is also possible that some of the positive reports are due to lung lesions other than the round foci.

Rountine sanatorium care was administered for all of the patients except the 2 with progressive lesions in whom pneumothorax was tried.

As these round foci were present when the patients were first seen, the pathogenesis was not clearly evident. However, in one case the history stated that the round focux was located at the site of an original cavity and in 3 patients the round lesions were present in reëxpanded pneumothorax lungs; and in all 3, the pneumothorax had been instituted for cavitation and a positive sputum. The round foci were situated where the cavities were originally described and, from

the history and previous roentgenological findings, it was probable that a cavernous pulmonary lesion had preceded development of the foci. Figure 1 shows this type of case with a dense isolated round focus present at the site of the cavity for which pneumothorax was done.

Group B—Subgroup 1: This group included 3 patients. The round foci were similar in appearance to those in group A. However, these patients had no such lesions originally and on subsequent radiological examination, years after the onset and first film, a round infiltrate presented itself completely formed in an area of lung previously clear.

In these 3 cases single lesions were located in the apex, first and second anterior interspaces, respectively, and all were under 2.5 cm. in diameter. The foci appeared in 2 patients twenty-two and forty-eight months after the diagnosis of their preëxisting pulmonary tuberculosis (fibrotic apical lesions in the contralateral lung), and in the third case, that of a sanatorium nurse, twenty-four months after the start of her employment with a chest interpreted as normal. Figure 2 illustrates the appearance of a round focus two years after the onset of tuberculosis in a lung that up till then had no evidence of tuberculosis within it. All of the round lesions were isolated with no surrounding infiltration. A positive sputum appeared for the first time coincident with the round lesion in all 3 cases and thereafter it remained almost persistently negative.

There were no characteristic symptoms at the time the round foci were found. The nurse had fatigue, weight loss, wheezing and expectoration. One patient was asymptomatic and the third had slight expectoration and wheezing. Bronchoscopy in this latter case revealed inflammation of the tracheobronchial tree with a thick gray mucopurulent exudate and partial occlusion of the stem bronchus on the side of the lesion, due probably to a swelling of the extrabronchial lymph nodes.

All of the round foci showed subsequent changes with one diminishing slightly in size, another markedly decreasing until it almost disappeared, and the third enlarging to twice its original size before it became moderately smaller, showing a suspicious area of clearing.

Group B—Subgroup 2: This group contained 4 patients with single round foci and one bilateral case that will be included in group D. Four of the round lesions were in the second anterior intercostal space and one in the third interspace. Four of the foci averaged 2 cm. and one was 4 cm. in diameter.

These cases were similar to those in group B, subgroup 1, in that the circular focus appeared completely formed. However, the foci presented themselves in an area of lung that was the site of tuberculous involvement. This is demonstrated in figures 3 and 4. The intervening stages in their formation were not seen.

The antecedent area in 3 instances was a very minimal coalescent infiltrate; in another, a few small spots and linear strand (figures 3 and 4), and in the last case, mottled nodules became covered with the typical round homogeneous lesion. These areas were the site of resolution of an earlier more extensive lesion.

Each case had other minimal evidences of tuberculosis in the same or contralateral lung, except one with hilar node enlargement. Bronchoscopy in this patient revealed oedema and swelling of the mucous membrane and a diagnosis of extrabronchial pressure was made.

The round foci in this group were the most unstable. Two showed a decrease in size and in one it was a marked change. These patients have been persistently negative though one was positive at first. Two of the other foci followed a similar course, becoming at first smaller and more dense over a period of six to nine months, then showing a great increase to almost twice the original size of the circular lesion; and the third showed the round focus decreasing slightly in size over a period of two months after its appearance, and then it cavitated (figure 15, case 3). These 3 patients had positive sputa and received pneumothorax.

As in group A, the pathogenesis was not definite as the actual formation of the foci was not observed. However, the first appearance of positive sputa with the lesions in group B-1, the positive sputa in all but one of the cases in group B-2, the marked instability of the foci and the cavitation that occurred in 2 of them indicate an active parenchymal focus. The appearance and behavior of these lesions will be seen to be identical with those in group C and group D where the pathogenesis (tuberculous cavitation) was evident.

Group C: In 7 patients the spontaneous closure of a pulmonary cavity resulted in a round focus. In a patient with bilateral cavities (figure 7), closure occurred on one side spontaneously and on the other side with pneumothorax.

This group included two apical cavities, two in the first, three in the second and one in the third intercostal interspace. These cavities were usually small, with only one of 3 cm. width; six, 2 cm. in diameter, and one, 1 cm. wide. Half of the cavities had no surrounding infiltration and the others had a few nodules nearby. In all of the cases these contiguous nodules resolved much. Two patients had contralateral apical infiltration.

The cavity walls which were usually of moderate thickness and uniformly thick around the central cavity clearing, gradually became heavier. In two cavities, fluid levels were present. The central area of translucency filled and a circumscribed homogeneous dense area resulted, smaller in size than the original cavity, and the focus continued to become smaller and firmer. Figure 5 shows a cavity well filled with very heavy irregular walls around an area of clearing and with complete closure and filling, then (figure 6) a homogeneous round focus formed, which then retracted and became smaller. Just as commonly the cavity would enlarge to form a fresh uniformly dense circular area slightly (or infrequently much) greater in diameter than the original cavity before retraction or decrease in size occurred. In cases with fluid level the cavities gradually filled from below before final closure and retraction instead of the uniform wall thickening and shrinkage. Figure 12 illustrates a case with fluid level, the lower half of the cavity filled, and with spontaneous closure (figure 13) a round focus formed.

These cavities were present an average of seven months before they showed

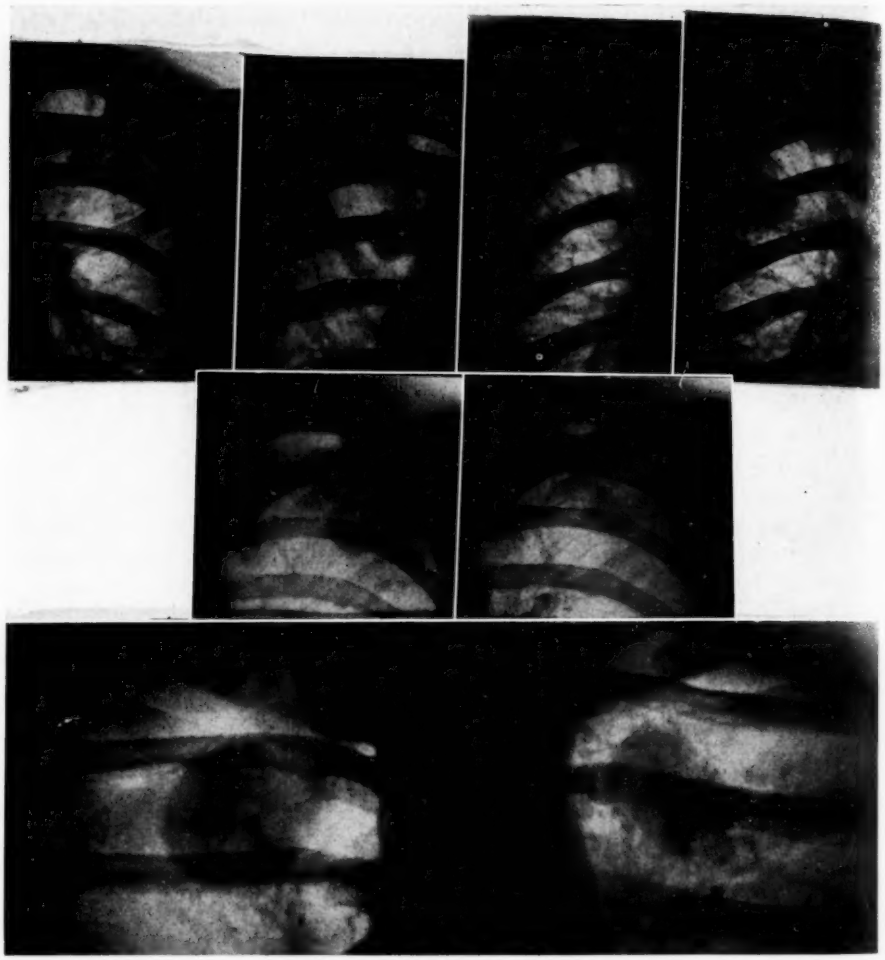

FIG. 1. (Upper row, 1st figure.) Case 1—Group A. *E. C.*, August 30, 1940. Fibro-calcific round lesion, left infraclavicular area. History of cavity left infraclavicular area and positive sputum for which pneumothorax was started left, September, 1935. Reëxpanded March, 1940. Negative since pneumothorax initiation.

FIG. 2. (Upper row, 2nd figure.) Case 2—Group B-1. *C. H.*, February 21, 1939. Dense round focus, right first interspace. Onset 1934. Lungs showed few fibro-calcific spots left apex and calcified hilar nodes left. Right side clear. Sputum negative. Unchanged until August, 1936, when round focus appeared in inner right first anterior interspace. Sputum positive for first time and for two months. During next five years round focus slightly smaller and more dense. Increased calcification left apex. Sputum always negative except once in April, 1938.

FIG. 3. (Upper row, 3rd figure.) Case 3—Group B-2. *R. G.*, February 28, 1941. Thin linear scar and few fine nodules in second right anterior interspace. Sputum negative.

FIG. 4. (Upper row, 4th figure.) Case 3. *R. G.*, April 14, 1941. Large round lesion over scar area. Sputum positive.

FIG. 5. (Middle row, left.) Case 4—Group C. *J. S.*, April 11, 1939. Thick-walled, well filled cavity, left infraclavicular area with irregular area of clearing within. Sputum Gaffky V.

FIG. 6. (Middle row, right.) Case 4. *J. S.*, October 25, 1939. Cavity completely filled

evidence of closure. The time required for the formation of the round focus averaged five months.

All of the round foci remained closed except one that within six months excavated again (figures 13 and 14). This case and 2 others had unsuccessful pneumothorax attempts, whereas the rest of the group continued on conservative care.

All but one of the patients had positive sputa on admission. The negative case remained persistently negative. Four of the others became negative with the formation of the round focus and remained so and the other 3 continued to have occasional positive cultures or sputa.

Group D: Eight patients had round foci form by the closure of a cavity by pneumothorax and one case with bilateral foci has been presented in group C and another in group B-2. Besides these latter 2 cases, all the others were unilateral with single round bodies except one with two foci. The round infiltrates were located twice in the apex and in all other cases (but for one in the third interspace) in the first anterior intercostal space.

The cavities were larger than in the other groups. Four of them averaged 3 cm., one was 2 cm. and another 5 cm. in diameter; in 2 the original cavity size could not be determined, as they were first seen after pneumothorax had been initiated.

Most of the cavities had small nodules or few linear strands or a small coalescent infiltrate in their vicinity. Besides the 2 cases with bilateral foci only one patient had contralateral disease.

The cavities had usually a moderately thick or very heavy wall. Only one of them presented a fluid level. The cavities were in various stages of closure before the pneumothorax was initiated. Six of the 8 patients had their pneumothorax instituted within a month after admission, one patient had it after four months and in the last one, a spontaneous pneumothorax had occurred.

The transformation of the cavity into a round focus occurred in half the cases within one month, in 3 patients in less than two months and in one case the round lesion was noted after a very complete pneumothorax was partially absorbed.

The formation of the round focus is a satisfactory result of the pneumothorax as it represents closure of a cavity. The early formation of the round focus indicates that a satisfactory collapse is often a partial one and occurs soon. The pneumothorax need not be increased very much beyond this partial stage. A careful collapse of the lung with subatmospheric pressure will often yield round foci and a proper selective collapse can be maintained and a maximum

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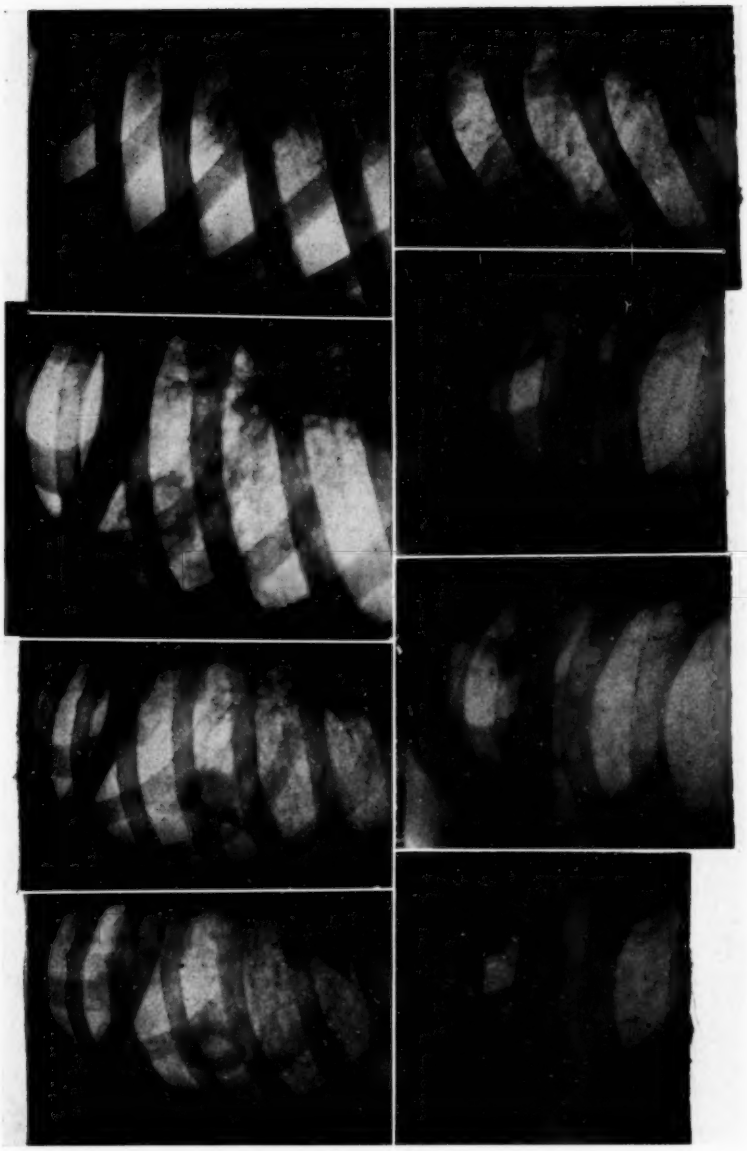
and retracted to form dense homogeneous round focus, left infraclavicular area. Sputum negative.

FIG. 7. (Bottom row.) Case 5—Groups C and D. *D. B.*, April 1, 1942. Lordotic view. Large bilateral apical round foci. On admission, December 11, 1941, very large apical thick-walled circular areas of infiltration with central irregular areas of clearing (apparently cavities). Sputum negative. Pneumothorax left, started December 15, 1941. Cavities formed homogeneously sharply defined round foci in both apices with partial pneumothorax left side, and spontaneous closure and retraction right side.



FIGS. 8-15

amount of functioning lung preserved. Figures 8, 9, 10 and 11 demonstrate the production of round foci from cavities in the presence of a partial pneumothorax collapse with no compression atelectasis of good lung and with sputum conversion.

The appearance in the formation of the round focus with pneumothorax is very similar to that seen with spontaneous closure of cavities. The difference is that the process occurs quickly with closure of the cavity by filling up and retention of material and collapse of the walls, and it appears as a homogeneous focus within the pneumothorax lung. Figure 7 shows the similar appearance in the round foci with closure of the cavities by pneumothorax or spontaneously. The round foci in figures 9 and 11 look like the round lesions in the other groups. As the pneumothorax increases the focus becomes smaller and it may disappear within the compressed lung. The actual closure may not be observed as the collapse may be rapid, but after reëxpansion, at the site of the original open vomica, a solid circular lesion is seen as the end-result of the cavity closure by pneumothorax.

All but one of the patients had a positive sputum. After pneumothorax and the formation of the round lesion by closure of the cavity, all but one became and remained negative. The exception was a case that remained positive until pneumothorax was instituted for the contralateral lesion, and since then the sputum has been often negative. This patient also had endobronchial tuberculosis diagnosed by bronchoscopy.

COMMENTS

Many ideas have been presented to explain this particular type of pulmonary tuberculous infiltration. The fact that there are so many theories indicates a lack of positiveness regarding pathogenesis.

FIG. 8. (Top row, 1st figure.) Case 6—Group D. *L. Q.*, January 19, 1940. Pneumothorax right, started January 17, 1940. Sputum Gaffky VI. Cavity of moderate size and thickness in partially collapsed right upper lobe.

FIG. 9. (Top row, 2nd figure.) Case 6. *L. Q.*, February 13, 1940. Partial pneumothorax right. Cavity now filled and appears as homogeneously round lesion. Sputum negative.

FIG. 10. (Top row, 3rd figure.) Case 7—Group D. *F. K.*, December 6, 1941. Large irregular thin-walled cavity, right infraclavicular area; scattered fine infiltration near it. Sputum positive.

FIG. 11. (Top row, 4th figure.) Case 7. *F. K.*, February 2, 1942. Pneumothorax right started December 18, 1941. Within pneumothorax lung, cavity now appears as homogeneously filled round focus. Sputum negative.

FIG. 12. (Bottom row, 1st figure.) Case 8—Group C. *R. B.*, September 14, 1935. Cavity right apex with lower half filled and fluid level present. Sputum alternately negative and positive.

FIG. 13. (Bottom row, 2nd figure.) Case 8. *R. B.*, January 17, 1936. Cavity spontaneously closed to form round lesion in right apex. Sputum negative.

FIG. 14. (Bottom row, 3rd figure.) Case 8. *R. B.*, December 3, 1936. Round focus has reopened to form cavity in right apex again. Cavity has been open for six months, with slight increase in size during this time. Sputum positive.

FIG. 15. (Bottom row, 4th figure.) Case 3. *R. G.*, June 17, 1941. Round focus in second right anterior interspace has excavated to form a large cavity. Small area of infiltration in axillary part of interspace. Sputum positive.

A majority of the writers have considered the round focus on an exogenous bronchogenic basis, an early or late stage in the development of reinfection tuberculosis. Their origin from a haematogenous dissemination has also been described. Others have reported them as part of a recessive phase of a primary infection. Their formation from a constitutional reaction has been explained with the interpretation that with tuberculin sensitivity and lowered resistance, pulmonary infection is manifested by caseation and destruction of tissue, but with good immunity and the lung refractory to bacillary invasion, the lesions become encapsulated and a stable round focus is produced.

This study has resulted in the formulation of the following opinions about the round focus.

None of the patients presented the typical picture of a primary infection of the lungs. Moreover, some had old hilar calcifications and many had additional parenchymal lesions. In 85 per cent of the cases, the round lesion was single and the great majority had no, or very scant, surrounding or additional infiltration. In no patient was there evidence of a characteristic bilateral symmetrical haematogenous pulmonary dissemination. Nor were there any extrapulmonary tuberculous conditions which would indicate a haematogenous source. These findings indicate that the round foci are reinfections that usually occur early and are of a bronchogenic nature.

The production of these characteristic foci could first be considered on an inflammatory basis. An exudative or pneumonic focus is the first manifestation of a tuberculous process in the lung, whether in a primary or reinfection phase. A pneumonic area could appear as a round lesion. Conceivably, the exudative elements could absorb and, with connective tissue replacement and contraction, a hard round lesion could result.

There are many reasons why we do not believe this to be the usual method of formation. The pathogenesis is related to tuberculous cavitation. In those cases with round lesions found completely formed (groups A and B) previous X-ray films revealed that a cavity had preceded the development of the focus in 4 cases. Positive sputum was associated with the lesions developing into the round focus in all patients in group B-1 and all but one in groups B-2, C and D. Conversion of the sputum usually resulted in the actual formation of the circular foci. The many variations in the size of the lesions are characteristic of cavities. Round foci can progress and shell out to form cavities. Most important of all is the fact that every case in this series that could be followed from the beginning through all the phases of production till the final appearance of the round focus showed the transformation of a tuberculous cavity into this special type of lesion.

Our cavities varied in size from one to 5 cm. Their formation into round foci usually occurred in a few months and resulted from spontaneous closure or as a consequence of collapse therapy. Changes in the circular foci were usually unrelated to the other parenchymal tuberculous lesions that may be present. Most of the cavities had heavy walls. This does not prove an old process, for the cavity contents may rapidly accumulate or become inspissated. Sweany (1)

has stated that "closure of the cavity is also affected by accumulation of granulation tissue on the inner wall of the cavity and contraction of the cavity by encroachment of this granulation tissue upon the lumen of the cavity."

There are many tuberculous pulmonary cavities but relatively few round lesions. The round focus represents only one form of cavity closure. Recently Auerbach and Green (2), in describing the pathology of clinically healed tuberculous cavities, stated that, in the closed method of closure, the lumen of the cavity becomes obliterated and replacement occurs by a scar or retention of caseous material. The cavity lumen, filled in and obliterated, forms an inspissated focus. They noted that cavity healing with inspissation of the caseous contents is the most frequent form found at necropsy. They reported that cavities that had closed according to X-ray evidence and appeared as dense, solid round shadows were, on necropsy, cavities the lumina of which were obliterated by inspissated material and which had no communication with the bronchi.

The foci on necropsy have been shown to be spherical bodies of thick caseocalcified structureless material enclosed in a dense connective tissue or hyalinized capsule of varied width, demarcated sharply, without surrounding tissue reaction or associated hilar node enlargement.

There has been considerable discussion and difference of opinion concerning the exact mechanism of cavity closure. Clinical and pathological material has been presented by many authors to demonstrate the essential condition to be either occlusion of the draining bronchi or the maintenance of open bronchi. It is agreed that closure can occur under both circumstances. In the 3 bronchoscopic examinations, done in our series, bronchial stenosis was described in each. However, as the round foci were already formed at the time of the bronchoscopies, the findings cannot be properly evaluated.

Three other patients had fluid levels in cavities (an indication of bronchial stenosis). A check valve mechanism in the draining bronchi can prevent the closure and retraction of the cavity as the entrapped air increases in amount and tends to keep the cavity open or increase in size. A fluid level, however, does not necessarily indicate that such a mechanism will result or persist, since the bronchial stenosis can undergo changes in closure of considerable degree. Our cases with fluid levels formed no check valve and all the cavities closed readily within six to twelve weeks.

The small number of round foci would suggest that mechanical factors are not the only ones operative in the formation and closure of cavities. To explain a single, closed cavity without surrounding infiltration, without immunological considerations, would be difficult. The extent and type of tuberculous infection is always related to the resistance or allergic response of the individual and the virulence and number of infecting organisms. The initial exudative phenomena of all tuberculous infection may proceed to absorption, caseation, fibrosis or calcification, depending on the predominance of resistance or infection. It is interesting to note that of our 55 patients, 85 per cent were white. This is in agreement with the experience that the Negro does not as often as the white

person have the power to localize his tuberculosis; he has the tendency to form acute, rapidly spreading disease and lymph-haematogenous disseminations.

The fully formed solid focus can increase or decrease homogeneously. Eighty-two per cent of the lesions were unchanged or became smaller. The round focus, by absorption of its exudative elements or inspissation of its contents and progressive fibrosis, or even calcification, can gradually retract and diminish in size. If bronchial occlusion occurs the contraction is increased, as the atelectatic shrinkage is within an area that has lost its normal elastic property. As noted, surrounding infiltration about the round lesions is rare. Thus the uninvolved lung parenchyma, by compensatory emphysema, fills in the potential space created by the shrinking focus.

However, the lesion may enlarge markedly or excavate. Fresh inflammatory tissue may appear around the lesion. The extent of this perifocal reaction may be altered by the allergic response of the lung parenchyma. The other influence is the increase in atelectasis of the perifocal tissues.

Softening or liquefaction may occur within the body of the focus. This may be combined with variations of the degree of closure of the draining bronchi, and the amount of drainage and size of the lesion will be affected. The closure and opening of the cavity in figures 12, 13 and 14 might be explained by changes in the draining bronchi. A previously closed bronchus may open, partially or entirely, and a patent bronchus may become occluded. Evidence of these changes is seen in our patients. In one case a round focus excavated and then closed to form a round lesion again, and in others, a cavity closed to form a circular focus which later reopened. The initial and final lesions in these patients were very similar in appearance. Other round foci enlarged or cavitated and caused progressive tuberculosis. Figures 14 and 15 present round foci that have cavitated. Occasional positive sputa may also indicate changes in drainage.

Variations of these factors (pathological changes in the body of the focus, degree of atelectasis, perifocal inflammatory reaction and condition of and changes in the draining bronchi) would explain the differences in the size of the foci.

Though the majority of the round foci remain unchanged or become smaller, this is only a temporarily benign lesion. Five patients, or 9 per cent of our cases, had cavitation and 2 of these, progressive tuberculous lesions. Another 9 per cent had, at their last examination, enlargement of the focus (2 of slight and 3 of marked degree, with one containing an area of increased translucency, suspicious of cavitation). These, and the other cases, may show additional changes at a later date. The lesions in all the groups are capable of this behavior. The round focus can cavitate after a few or many months of stability, (extremes of two to twelve months in our cases). Tubercle bacilli have been found in these inspissated, caseous, or even partly calcific round foci, or healed cavities on necropsy, and they remain a source of danger. Only 36 per cent of our cases were always negative. The many patients with only occasional positive sputa and the frequent variations in size indicate an unstable lesion that can progress.

Only 13 per cent of the lesions were in the apex proper. The great majority of the foci are situated in the infraclaviclar area and above the level of the second anterior interspace. It has been noted by Douglas, Nalbant and Pinner (3) that subapical disease is frequently acute in onset, pneumonic in nature, progressive with excavations, often formed within six months, and characterized by acute clinical changes in comparison to insidious, productive, slowly changing or benign apical infiltrations.

This focus should be checked as often as any tuberculous cavity, for frequent examination is the only method by which early changes can be noted. These cases require no special treatment while stable, but careful observation. An increase in the focus often precedes actual cavitation or progression. Should any enlargement of the focus occur, or progression, or cavitation, collapse therapy should be instituted, the type depending on individual variations. Bed-rest does not promise the immediate control of the lesion that is required.

SUMMARY

1. A clinical roentgenological study of 55 patients with round tuberculous pulmonary foci has been presented.

2. The formation, characteristics and behavior of these lesions have been described.

3. It is our belief that they are the end-result of tuberculous cavitations.

4. Though usually benign, round foci are capable of cavitation and progression, even after long periods of time, and must be carefully observed.

SUMARIO

1. Preséntase un estudio roentgenológico clínico de 55 enfermos en que había focos tuberculosos redondos del pulmón.

2. Se describe la formación característica y comportamiento de esas lesiones.

3. Opina el autor que las mismas representan el resultado terminal de cavernas tuberculosas.

4. Aunque por lo general benignos, los focos redondos son susceptibles de cavitación y evolución, aun tras períodos prolongados de tiempo, y deben ser cuidadosamente observados.

The author gratefully acknowledges the coöperation and assistance of Gladys F. Tordik, Occupational Therapist of the Municipal Sanatorium, and the patients in the photographic division of the Rehabilitation Department for their kind preparation of all the photographs.

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ROENTGENOLOGY OF THE DIGESTIVE TRACT IN THE TUBERCULOUS [1,2]

JOHN L. KANTOR[3]

The roentgenological examination should constitute an integral part of a comprehensive gastrointestinal survey of tuberculous patients. As such, it may reveal conditions either entirely independent of, or specifically related to, the tuberculous process. This discussion will be limited to the specific lesions of the digestive tract.

OESOPHAGUS

Intrinsic tuberculous lesions of the oesophagus are rare. The following brief description of specific ulcerative oesophagitis is reported from the Pathological Department of the Montefiore Hospital.

A man, age seventy-one, was admitted August 6, 1929 and died seven weeks later of chronic pulmonary tuberculosis; tuberculous laryngitis, oesophagitis, enteritis and proctitis; tuberculosis of the kidney and of the suprarenal glands. At autopsy the oesophagus appeared as follows: "At the cardia the mucosa is markedly thickened and corrugated in a longitudinal direction. Between the corrugations are areas of ulceration. Upon them the mucosa is white and thickened in appearance. There are long ulcers of 1 mm. or more in width extending up the oesophagus for a distance of over 10 cm. from the stomach." As far as known, the oesophagus of this patient was not X-rayed during life.

We have had instances of surprise findings of a nonspecific ulcer of the oesophagus at autopsy in nontuberculous patients in whom the condition likewise was not diagnosed before death. It is therefore suggested that the oesophagus be included in the roentgenological survey whenever possible.

In addition to intrinsic oesophageal lesions we have encountered many cases of dysphagia due to mediastinal adhesions involving the oesophagus. Perhaps most, if not all, of these abnormalities can be demonstrated on roentgenological examination, provided the oesophagus is thought of and included in studies of the digestive tract.

STOMACH

Tuberculous lesions of the stomach are rare. Only 368 cases were reported in the literature up to 1938, according to Clagett and Walters (1). In a series of 71,871 unselected autopsies reviewed by Good (3), the incidence of gastric tuberculosis was 0.34 per cent and in 7,416 consecutive gastric operations performed at the Mayo Clinic gastric tuberculosis was encountered in 3 cases.

[1] 1942 National Jewish Hospital William S. Friedman Lecture, delivered at Colorado University School of Medicine, Denver, Colorado, November 3, 1942.

[2] Permission for publication granted by the War Department Manuscript Board, November 21, 1942.

[3] Colonel, Medical Corps, U. S. Army.

In autopsies on patients dying of tuberculosis at Montefiore Hospital in the last twenty-five years, gastric tuberculosis was found in 2 cases. One of these was a tuberculoma, the other an ulcer with tuberculous infiltration, located at the margin of a gastroenterostomy stoma.

In none of these cases was the diagnosis made during life by X-ray examination. In the case of the tuberculous gastric ulcer at the margin of the gastroenterostomy stoma, the X-ray appearance was interpreted as being suggestive of a small obstructing neoplasm and the possibility of "adhesions following ulcer" was mentioned.

These errors of commission and omission are reported to stimulate interest and effort on the part of roentgenologists. In every gastric lesion in a tuberculous individual the possibility of tuberculosis of the stomach should be given careful consideration.

THE SMALL INTESTINE

Because the small intestine was the last great division of the digestive tract to be subjected to X-ray study, it offers an interesting and promising field to the roentgenologist. The use of large films (14 by 17 inches) and the "fractional" method of observing the progress of an opaque meal through the small intestine have made possible a more precise diagnosis of conditions hitherto overlooked or only suggested. One has only to scan the recent literature on small intestinal tumors, regional ileitis and steatorrhoea to be convinced of the advances made in this direction.

TABES MESENTERICA

When the lacteal drainage of the small intestine is so damaged by tuberculous disease of the mesenteric lymphatics that fat absorption is impaired, steatorrhoea may result. This steatorrhoea is sometimes called idiopathic, because the trouble is in the absorbing mechanism and not in defective fat splitting by pancreatic ferment. The condition is comparable to that occurring in sprue, celiac disease, lymphosarcoma of the intestine or of the mesenteric lymphatics or other diseases in which mucosal absorption is damaged. It has been shown (Kantor (4, 5)) that in many, though not all cases of idiopathic steatorrhoea X-ray study of the small intestine reveals characteristic changes in the mucosal pattern.

These changes, to which the name "moulage sign" has been given, consist in the ironing out of the *valvulae conniventes* in loops of the jejunum and occasionally in the duodenum as well, an appearance that once seen can be readily recognized.

The roentgenological technique is simple in principle, although it involves frequent observation of the passage of a standard opaque meal through the entire small intestine and the use of large films. The period covered is usually from three to nine hours after the ingestion of the opaque meal. Under ideal conditions, the examination should be continued until the small intestine is empty. The frequency with which films are taken varies from every fifteen

minutes at the beginning of the study to every one to two hours when the ileum is being traversed.

Descriptions of roentgenological changes in the small intestine, similar to the "moulage sign," have already appeared in case reports of wide-spread abdominal or intestinal tuberculosis. Such changes have been attributed to "deficiency states" without mention of steatorrhoea. It would be very desirable to have faecal fat studies made simultaneously with intestinal roentgenological investigations in all cases where *tabes mesenterica* is suspected.

TUBERCULOUS ENTEROCOLITIS

Tuberculous ulcers of the intestines are located chiefly in the ileo-caecal region, but other parts of the bowel may be affected. Thus, in a survey of U. S. Veterans' Bureau material, Matz (7) reports the following localizations in order of frequency: caecum 52 per cent, ileum 39 per cent, ascending colon 32 per cent, ileocaecal valve 15 per cent, descending colon 11 per cent, jejunum 8 per cent, the appendix 7 per cent, duodenum 6 per cent, rectum 4 per cent, sigmoid 3 per cent. Tuberculosis of the peritoneum was found in 8.5 per cent.

Tuberculous ulcers high in the small intestine were also found occasionally in the Montefiore Hospital experience. The following autopsy reports are abstracted from the protocols of the Pathological Department. In the patient with tuberculous ulcers of the oesophagus already referred to, intestinal ulcers began as a few scattered, ragged, punched-out areas in the jejunum and increased in number until the ileocaecal valve was reached. In another case a nodule, 6 cm. in diameter, with a central ulcerated area was found 1 cm. distal to the pyloric ring. The edges of this ulcer were elevated and slightly undermined. More distally, several smaller nodular ulcerated areas were found so that about ten of these lesions were present in the duodenum. In the jejunum the lesions, which were located at widely separated intervals, were similar in size and appearance to those in the duodenum. In the ileum these lesions became larger, ran in a transverse direction, and the ulcerated portions were deeper and showed evidence of haemorrhage.

As far as I know, no antemortem diagnosis of tuberculous ulcers of the duodenum or jejunum has yet been made. Perhaps better results might be obtained from detailed roentgenological studies of this part of the small intestine with films taken at frequent intervals.

Up to now, the roentgen method gives returns of greatest practical value in the diagnosis of tuberculous enterocolitis in the ileocaecal region, but the results are not as accurate as one might wish. Thus, in a carefully controlled series of 67 cases observed at Montefiore Hospital by Steinbach (8), in which the roentgenological findings were controlled at necropsy, it was found that in only 32 instances, or in 48 per cent, the results of both methods coincided precisely. In 35 cases (52 per cent) there was disagreement between the two methods. In 3 of these cases the roentgenological picture was interpreted as intestinal tuberculosis, but at nectopsy the gut was found free from such disease. In 18 cases, the roentgen picture indicated a healthy gut, but necropsy showed ulceration of

the intestines. In 6 cases in which autopsy showed disease, the X-ray findings were indefinite, whereas in 4 cases which came to necropsy with unaffected intestines the roentgen reports were likewise indefinite. Finally, in 4 cases in which the X-ray examination suggested tuberculosis of the caecum, the necropsy showed that the lesions were in the small intestine instead.

What is the reason for such a relatively poor showing and how can the roentgen diagnosis of intestinal tuberculosis be improved? Before answering these questions certain basic principles may be reviewed with advantage.

In the first place, contrary to the situation in the case of the stomach and duodenum, individual ulcers in the lower intestine cannot be demonstrated roentgenologically. The diagnosis is therefore presumptive and is usually based on indirect signs, although in certain cases direct findings may be available. The indirect signs refer to the increased irritability or spasm of areas in which ulcers are most likely to be present. This is the basis of the well known Stierlin phenomenon, in which filling of the caecum or caecocolon is defective in the presence of stasis in the ileum and increased transport through the ascending and transverse colon.[4] Such observations are best made by serial films of sufficient size taken between five and nine hours after the ingestion of a standard opaque meal. In fact, we regard the "nine hour film" as the most valuable single observation. Demonstration of irritability of the proximal colon can likewise be made in theory by the use of the opaque enema, but since filling proximally to the hepatic flexure is not always accomplished, even in nontuberculous subjects, owing to extraneous factors such as general irritability of the colon, this technique is not of such great practical value as is the progress meal.

In utilizing the method of indirect signs for the diagnosis of intestinal tuberculosis, certain conditions must be laid down. The first requirement is that the area of defective filling due to irritability or spasm involve the caecocolon, that is, the region where tuberculous ulceration is most likely to exist. Irritability of the colon distal to the hepatic flexure is characteristic of colonic instability in general, a functional condition common to nontuberculous as well as to tuberculous individuals, and wholly independent of organic bowel disease. Therefore, if the proximal colon is not affected, tuberculosis can be excluded, whether the distal portion is involved or not.

Second, irritability of the suspected segment must be shown to be constant or at least repeated. This can be assured by taking a sufficient number of films at proper intervals as already described, and best of all, by repeating the entire examination, if possible, on different occasions. This precaution is not always taken and it is likely that too many diagnoses of intestinal tuberculosis are attempted from single observations.

Finally, persistent irritability or spasm of the caecum may be a manifestation of disease localized in the terminal ileum without any involvement of the colon whatever. This has been shown to be true for tuberculosis by Steinbach as

[4] It should be mentioned in passing that the Stierlin sign, though suggestive, is not always pathognomonic of tuberculosis, inasmuch as it may be caused by organic disease of nontuberculous character.

already mentioned, as well as by others, and I have seen the same phenomenon repeatedly in cases of terminal nonspecific ileitis. Therefore, in reporting cases showing ileo-caecal irritability it is safer to use such an expression as "probable ileocaecal tuberculosis," instead of attempting a more precise anatomical location of the disease.

Before taking up the direct methods of X-ray diagnosis in this field, certain general aspects of the reliability of the X-ray method may be discussed. In my opinion, a failure in making a negative diagnosis of intestinal tuberculosis (that is, reporting no intestinal tuberculosis when such exists), is not nearly so grave an error as is the opposite. The reasons for this statement are, first, that any organic lesion may exist without giving X-ray manifestations just as it may occur without producing clinical symptoms; and second, that intestinal ulceration, though not present at the time of X-ray examination, may develop subsequent to that time. On the other hand, making a positive roentgen diagnosis of intestinal tuberculosis when the disease cannot be demonstrated at autopsy, should be charged up as an X-ray failure, because it is unlikely that a patient dying of pulmonary tuberculosis is capable of healing an intestinal involvement in the interval between the X-ray examination and his demise. Obviously, errors in positive diagnosis are likely to cause lack of confidence in the roentgen procedure.

The direct diagnosis of intestinal tuberculosis is based on the demonstration of roentgen abnormalities caused by the lesions themselves. Such appearances are rare and when they do occur usually represent complications of the ulcerative process, rather than the simple ulcer itself. Thus, in the caecum the disease may assume the hyperplastic variety due to the development of productive inflammation in the bowel walls causing deformity therein as well as narrowing and irregularity of the lumen—in short, a tuberculoma. In this case the roentgenological pattern is very well defined and constant, corresponds to a palpable tumor, and is demonstrable by any procedure that will fill the affected area with opaque substance, be it administered by mouth or by rectum. The only caution to be observed in this condition is that the X-ray picture is generally indistinguishable from carcinoma and the differential diagnosis is usually to be made on additional clinical data, if it can be made at all short of exploratory operation or autopsy.

A still rarer type of objective roentgenological evidence may be observed when ulceration of the terminal ileum is complicated by peritoneal involvement (peritonitis). This latter may be represented by adhesions with or without perforation of an underlying ulcer. In such cases the involved loops of intestine may appear abnormally fixed and static on repeated observations and their outlines may assume bizarre and jagged configurations, instead of the usual smooth and symmetrical contours. Here again, the precise diagnosis is based on the constancy of the roentgen picture and serial roentgenograms are most important. Finally, it should be noted that the above findings are not necessarily peculiar to tuberculous peritonitis, but may be found in peritonitis from other causes.

It will be observed that no precise statement has been made about the roentgen diagnosis of tuberculous ulceration of the terminal ileum as such, that is, uncomplicated by tuberculous involvement of the overlying peritoneum. This is because it is felt that the oft-cited dictum that ileac dilatation and stasis are indicative of ileac tuberculosis is in my opinion far from universally valid. Indeed, the finding of ileac stasis by itself is hardly peculiar to ileac tuberculosis. It can occur, for instance, in colonic irritability from any cause, also in the congenital anomaly known as non-descent of the caecum and, not infrequently, following operation for appendicitis. Only when it is associated with defective filling of the caecum in the form of the Stierlin phenomenon is it suggestive, though not absolutely indicative, of tuberculosis, and then, as already mentioned, the tuberculosis may be located either in the caecum or in the terminal ileum.

DIFFERENTIAL DIAGNOSIS

The importance of distinguishing between tuberculous enterocolitis and the unstable colon has been stressed. The distinctive characteristics of tuberculosis are that the caecocolon is always irritable, and in cases of tuberculoma the deformity is of a fixed and constant pattern. A universal colitis, that is, irritability of the entire colon, including the caecocolon, may occur in tuberculosis, but it may also be due to other causes. In such cases, it is suggested that the roentgen report read "universal colitis compatible with intestinal tuberculosis." In the unstable colon on the other hand, the irritability is usually confined to the region distal to the hepatic flexure, the entire appearance changes constantly with alterations in autonomic nervous tonus, and there is never a localized area of deformity of contour.

The differentiation of tuberculous from idiopathic ulcerative colitis is usually not difficult. In the latter condition, the distal colon is the region first involved. In the earliest stages "fuzzy" bowel outlines occur, then loss of haustra and development of "sausage spasm," and finally universal narrowing and shortening of the colon with rigidity of the walls and assumption of the "tape" or "band" appearance so characteristic of late involvement. When, as may rarely happen, the idiopathic colitis is limited to the proximal colon, greater difficulty may be experienced, and the distinction between the two diseases may have to be made on other than roentgenological grounds, such as the presence or absence of pulmonary tuberculosis.

A most interesting differential diagnosis is that between tuberculous ulceration of the terminal ileum and regional (terminal) ileitis. Up to the appearance of the classic paper of Crohn, Ginzburg and Oppenheimer (2) in 1932, in which the pathology of ileitis was clearly demonstrated, this condition was frequently mistaken for tuberculosis. In fact, several of our cases of proven ileitis at the Montefiore Hospital were originally admitted to the tuberculosis service. Even the histopathology of the two conditions is confusing, as tubercles and giant cells may occur in regional ileitis. However, tubercle bacilli are demonstrable only in tuberculous lesions, never in ileitis. With the description of the roentgenological characteristics of regional (terminal) ileitis (Kantor (6)), it has become

a relatively simple matter to differentiate the two conditions before operation or autopsy. The roentgen criteria for nonspecific ileitis have been rather widely accepted and may be succinctly described as follows:

1. In films taken from five to nine hours after a barium meal, in patients with ileitis, there is a "filling defect" in the right iliac fossa just proximal to the caecum due to the presence of the thickened loop or loops of diseased terminal ileum, which contain practically no barium (see paragraph 4 below). This "filling defect" is absent in tuberculosis where barium containing loops of ileum show practically continuous filling right up to their entry into the caecum.

2. The last filled loop of ileum often shows fixed deformity in contour, in ileitis, usually a tapering in the direction of the obstructed segment.

3. There is dilatation of ileac loops proximal to the "filling defect" in ileitis. In tuberculosis, dilatation of ileac loops, if present, is irregularly distributed and often involves the terminal small intestine.

4. The important finding in ileitis, when present, is the "string sign." This has the appearance of a thin, irregular, extremely narrow, string-like streak of barium extending more or less continuously from the region of the last visualized loop of ileum through the entire extent of the filling defect up to the ileocaecal valve. It is characteristic of the string sign, which may be multiple in case of extensive involvement or fistula formation, that it represents a fixed pattern. The string sign has not been observed in intestinal tuberculosis.

SUMMARY

1. The roentgenological examination should constitute an integral part of the gastrointestinal survey of tuberculous patients in order to reveal digestive conditions due to, or independent of, the underlying specific infection.

2. Rare tuberculous lesions of the oesophagus, stomach and upper small intestine are still being missed on roentgenological examination but may be revealed in the future by greater attention to detail or by basic improvements in technique.

3. The X-ray may be of value in the diagnosis of tabes mesenterica when steatorrhoea is present. In such cases, the "moulage sign" may be present as in other forms of steatorrhoea of the idiopathic variety.

4. The greatest field of usefulness for the X-ray is in the diagnosis of tuberculosis of the ileocaecal region (tuberculous enterocolitis). At present the results are not brilliant, mistakes being made in both positive and negative diagnosis.

5. Errors in negative diagnosis, that is, X-ray negative, autopsy positive, may be excusable, but mistakes in positive diagnosis cause loss of confidence in the value of the roentgenological procedure.

6. Errors in roentgenological diagnosis are usually due to insufficient study, inadequate technique, or failure to make a differential diagnosis.

7. The diagnosis of intestinal tuberculosis is based on indirect and direct findings. To bring these out most advantageously, roentgenograms should be made on large films at frequent intervals following an opaque meal, especially from five to nine hours after ingestion.

8. In order to be diagnostic of tuberculosis, an area of spasm or irritability should involve the caecocolon, should be constant or at least repeatedly present in several films made at proper intervals and, if possible, should be confirmed at subsequent examinations.

9. A tuberculoma is characterized by a fixed pattern of localized deformity of the caecocolon, corresponding in position to a palpable tumor.

10. The most important conditions from which intestinal tuberculosis should be distinguished are the unstable colon, idiopathic ulcerative colitis, cancer and terminal (regional) ileitis.

SUMARIO

1. El examen roentgenológico debe constituir parte integrante del estudio gastrointestinal de los tuberculosos, a fin de revelar los trastornos digestivos debidos a, o independientes de, la infección específica subyacente.

2. Con el examen roentgenológico todavía se pasan por alto raras lesions tuberculosas del esófago, estómago y porción superior del intestino delgado, pero pueden descubrirse en el futuro prestando más atención a los detalles o mejorando fundamentalmente la técnica.

3. Los rayos X pueden ser útiles en el diagnóstico de la tabes mesentérica cuando existe esteatorrea. En esos casos el "signo del moulage" puede estar presente como sucede en otras esteatorreas del tipo idiopático.

4. El campo máximo de utilidad de los rayos X es para el diagnóstico de la tuberculosis ileocecal (enterocolitis tuberculosa). Hasta ahora los resultados no han sido brillantes, discutiéndose los errores de diagnóstico tanto en sentido positivo como negativo.

5. Los errores negativos, es decir, roentgenografías negativas y autopsia positiva, pueden tener disculpa, pero los positivos hacen perder la confianza en el valor de la roentgenografía.

6. Los errores en el diagnóstico roentgenológico suelen deberse a insuficiente estudio, técnica inadecuada, o descuido en el diagnóstico diferencial.

7. El diagnóstico de la tuberculosis intestinal se basa en hallazgos indirectos o directos. Para obtener éstos en la forma más provechosa, deben obtenerse roentgenogramas en películas grandes a plazos frecuentes, después de una comida opaca, y en particular, de 5 a 9 horas después de la ingestión.

8. Para considerarlo como diagnóstica de tuberculosis, una zona de espasmo o irritabilidad debe comprender el ciego y colon, debe ser constante o por lo menos estar repetidamente presente en varias roentgenografías obtenidas a plazos apropiados, y si es posible debe confirmarse en los exámenes subsecuentes.

9. Un tuberculoma caracterízase por un patrón fijo de deformidad localizada del colon y ciego, correspondiendo en su posición a un tumor palpable.

10. Los estados más importantes, de los cuales hay que diferenciar la tuberculosis entérica, son: inestabilidad colónica, colitis ulcerada idiopática, cáncer e ileítis terminal (regional).

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PECTIN AGAR FEEDING IN TUBERCULOUS ENTEROCOLITIS[1,2]

PAUL D. CRIMM, J. J. WESTRA AND RUTH E. THOMPSON[3]

Intestinal tuberculosis, as a complication of pulmonary tuberculosis, continues to be one of the major unsolved problems confronting the phthisiologist. It is important because of its frequency and because of the serious threat it offers to the recovery of the patient from his pulmonary disease. The incidence of intestinal tuberculosis at autopsy, of patients with pulmonary tuberculosis, has been reported variously as being as low as 30 per cent and as high as 92 per cent. The average of most large series reported is about 70 per cent. In the routine investigation of 1,801 sanatorium patients at the Trudeau Sanatorium, Brown and Sampson (1) found 148 with intestinal disease, of which 1 per cent (4) occurred in 355 cases with minimal disease, 9 per cent (99) in 1,100 cases with moderately advanced and 26 per cent (45) in 175 far advanced cases. In a similar study of 1,336 white and 385 Negro patients, Brock and Perry (2) found intestinal involvement in 1 per cent of 95 minimal cases, in 6.6 per cent of the 467 moderately advanced patients and in 18.1 per cent of the 774 patients with far advanced disease. The latter workers, on the basis of the comparison of their percentages since 1930 with those of the Trudeau series compiled prior to that date, are of the opinion that the incidence of intestinal tuberculosis is definitely on the decline.

The seriousness of intestinal involvement, as a complication, has been recognized by all workers who have studied the disease. Until the careful studies of Brown, Sampson and others, the disease was recognized only in the terminal stages and was considered as portending a hopeless outlook. Even in the cases of earlier, less extensive involvement, with fewer symptoms, the intestinal disease presents a serious threat to recovery from the pulmonary disease. The old sayings coined by Lawrason Brown have it that "the road to recovery lies through the stomach," that "the best friend of a consumptive is a good digestion," and that "digestion is the keystone of the prognostic arch." Tuberculous involvement of the intestine, by interfering with adequate ingestion, digestion and absorption, interposes a formidable barrier in this road to recovery. In addition, the fever which so frequently accompanies the intestinal complication, further increases the rate of metabolic processes, and the pain and diarrhoea interfere with the patient's rest.

Numerous procedures, singly or in combination, have been used in the treatment of intestinal tuberculosis. These include the use of a smooth, low cellulose, high caloric diet, which has been employed by most workers; the addition to the diet of large amounts of vitamins A, D, and C in the form of cod liver oil and tomato juice by McConkey (3), natural and artificial heliotherapy, the

[1] From Boehne Tuberculosis Hospital, Evansville, Indiana.

[2] Read before the Mississippi Valley Conference on Tuberculosis, Chicago, September 18, 1942.

[3] Dietitian.

parenteral injection of large amounts of calcium as the chloride or gluconate and the use of various antispasmodic drugs, such as Trasentin (Cherry (4)). In our experience an excess of calcium, vitamins D and C, does not augment the cure of tuberculous lesions.

Because of the numerous reports of satisfactory results obtained by the use of Pectin Agar in the treatment of diarrhoea in infants and children, it seemed of interest to us to determine the value of this preparation in the treatment of intestinal tuberculosis. It was thought that the claimed actions of pectin and agar in producing formed stools, favoring normal peristalsis and absorption and adsorption of bacteria with their toxins would favor the healing of the ulcerative lesions.

METHOD OF STUDY

The patients included in this study were patients with pulmonary tuberculosis, who presented obvious, or questionable symptoms of intestinal involvement. The symptomatology of intestinal tuberculosis is complex and deserves some detailed consideration.

The earlier symptoms are usually referable to small-bowel lesions, and include nervousness and irritability, poor appetite that is not so much a distaste for food as an appetite too easily satisfied, dyspepsia, flatulence, constipation, nausea and vomiting and vague epigastric distress. Stewart (5), in his excellent summary, *Theses on Intestinal Tuberculosis*, states, "These symptoms, nervousness, slight impairment of appetite, and constipation beyond usual, form, in our experience, the most valuable early diagnostic triad." The later symptoms probably due to large-bowel lesions, are diarrhoea, abdominal pain and terminally, bloody stools. An additional important symptom is fever, when this is not explained by some other complication.

In this study, the presumptive diagnosis on the basis of symptoms and physical findings, was confirmed by roentgenoscopic and roentgenographic examination with a barium meal and a barium enema. (Of these two procedures, the barium meal, in our experience, affords much more information than the barium enema, and in some cases was the only procedure used.) The following signs were looked for in the examination: Stierlin phenomenon (absence of filling of the caecum while the terminal ileum and transverse colon are filled), spastic filling defects, filling defect with palpable tumor, persistent irregularity of the caecum, or persistent mottling after reëxamination of caecum and ascending colon, segmentation, dilation, matting or adherence of ileal loops. In questionable cases, observations were made at frequent intervals, and often the whole examination was repeated. Of the signs mentioned, the appearance of the caecum is perhaps the most important. As noted by Stewart (5), "a ragged, dwarfed, shrivelled caecum, a caecum that does not fill, or that empties quickly, that seems intolerant of barium, pretty much makes the diagnosis."

The criteria employed in determining the effectiveness of Pectin Agar were (*1*) decrease in the severity of the symptoms, (*2*) increase in weight, or in the ability to maintain weight, instead of losing progressively and (*3*) improvement in the appearance of the bowel on X-ray examination.

Twenty-four patients, of whom 20 had far advanced and 4 moderately advanced disease, are included in this study. Of these patients, 16, or 66.6 per cent, had a positive sputum. There were 14 males and 10 females. Some of these patients were extremely ill, with a hopeless outlook, but were included as a critical test of the value of Pectin Agar in controlling the intestinal symptoms.

DIET AND PREPARATION OF PECTIN AGAR

The diet given these patients was the so-called smooth, or low cellulose diet. Vegetables high in cellulose were entirely omitted. The others were served pureed. Only fruits with low cellulose content were used. Pork except bacon was excluded. Chicken, fish and ground meat were served. Custards, simple puddings, plain cake, toast, milk, fruit juices, finely milled cereals, macaroni, spaghetti and noodles constituted the chief items of the diet.

The Pectin Agar used in this experiment[4] can be flavored and sweetened to suit the taste of the individual. It is hard to get it into a smooth solution unless the Pectin Agar is added very slowly. The lumps do not cook out, even if the mixture is stirred all the time it is cooking. They will not beat out after cooking. We have found that if we add the Pectin Agar to the fluid very slowly and beat thoroughly with a rotary beater before cooking, the product is smooth.

We have had very little success offering the product in any other form than liquid. It is not sufficiently disguised if offered in combination with a food. If offered by itself as a pudding, the patients send it back with the complaint that, though it tastes all right, they cannot swallow it. They chew and chew, but it won't go down—it tastes and acts like rubber, etc.

Preparation of this product with vanilla malted milk has been one of the best methods of utilization. The product, after it is cooked, does not become as hard and rubbery as do other flavors with exactly the same amount of Pectin Agar and fluid (Product № 102, 1½ tbsp. to 16–20 oz. fluid). It may be stirred into additional milk or water and makes a drink that can be easily taken. Chocolate and lemon also have been used successfully. Pineapple juice and grape juice dissolve the Pectin Agar much more readily than either water or milk. These fluids form a smooth suspension which does not need to be beaten if the Pectin Agar is added reasonably slowly. This form must be melted over hot water before use, if it has been prepared more than one hour before it is to be used. The liquid may be poured over chipped ice and makes a reasonably palatable drink.

RESULTS

Of the original 24 patients, 8, or 33.3 per cent, died in the hospital; 10, or 41.3 per cent, have apparently recovered from their intestinal disease; 2, or 8.3

[4] Preparation was made for us by Mead Johnson and Company (citrus pectin grade 100 and a good quality of agar agar was employed). After our work was completed we were advised by the company that all stocks of agar agar have been frozen by the War Production Board and that, pending satisfactory solution of agar supply, they cannot furnish further quantities for observation.

per cent, are improving and still under treatment, and 4, or 16.6 per cent, left the hospital against advice before studies could be completed.

Of the 8 patients who died, 5 expired within ten weeks of the time Pectin Agar feeding was begun. These patients all had far advanced tuberculosis, with consistently positive sputum. Three of them also had laryngeal tuberculosis as a complication. The extent and character of the pulmonary disease in all of them were such that recovery, even without the intestinal disease, would be unlikely. However, varying degrees of symptomatic relief were obtained by 6 of the 8 patients, although their disease was too severe to allow recovery.

The 10 patients who have apparently recovered from their intestinal disease include 6 with far advanced and 4 with moderately advanced disease. One of these patients received Pectin Agar for three months, 6 received it from six to eight months and 3 were fed Pectin Agar for ten months to one year. All of these patients gained weight, the average gain being 13 pounds for the period of Pectin Agar administration. Some of them had previously received other treatment, such as artificial heliotherapy, or codliver oil and tomato juice, without improvement. The relief of symptoms with Pectin Agar was usually prompt and striking, so that excellent coöperation in the experiment was usually given. Later on when the patient is symptom free, it is a task to make him realize that he should stay on his diet. In one patient, Pectin Agar seemed to cause nausea and indigestion after having been fed seven months and was discontinued.

The following case history illustrates the gratifying results obtained with Pectin Agar and shows that recovery may occur in the presence of severe disease.

Case 6 (C.F.): Male, age twenty-five, who was admitted in December, 1939, with infiltration throughout the right lung and numerous small cavities, infiltration of the upper half of the left lung, with a cavity in the apex and laryngeal tuberculosis with complete aphonia. Sputum was markedly positive. Pneumothorax was instituted on the right December, 1939, and a paraffin pack was placed over the left apex in December, 1940. Gastro-intestinal symptoms appeared fifteen months later (March, 1941) and were progressive, with diarrhoea, distension, dyspepsia, anorexia, weakness and nervousness. X-ray examination on April 25, 1941 showed marked hyperperistalsis, with dilatation and segmentation in the small bowel, marked spasm and irregularity of the caecum and a filling defect in the hepatic flexure. Treatment with Pectin Agar was begun on May 7, 1941. The diarrhoea and other symptoms gradually subsided and the patient gained weight. Roentgenographic recheck six months later showed a decrease in hypermotility with disappearance of the spastic defect in the hepatic flexure and reappearance of haustra. A further recheck fourteen months after onset of treatment showed normal motility and no abnormality in the contour of the bowel. Pectin Agar was discontinued with no recurrence of his symptoms.

The 2 patients who are still under treatment both have far advanced pulmonary disease. In both of them, the intestinal symptoms which were preventing proper nutrition are well controlled and the patients are gaining weight in spite of a consistently positive sputum.

Of the 4 patients who left against advice, 3 were symptomatically improved while receiving Pectin Agar, although the status of the intestinal disease was

improved in only one of them on X-ray examination. These patients are all known to have died at home.

COMMENT

Necropsy of the 8 patients who died revealed extensive tuberculous ulcerations of the bowel. There was also extensive caseo-ulcerative pulmonary disease in 7 cases and fibrocaseous disease in one case. In 3 cases there was severe tuberculous disease of the larynx. Microscopical examination of the pulmonary and intestinal lesions revealed a similar pathological process, characterized by little or no evidence of healing.

As emphasized by Rubin (6) in his extensive correlative study of pulmonary and secondary intestinal tuberculosis, patients with far advanced disease of this fulminating type die irrespective of their complications. Most of these patients were extremely ill when Pectin Agar feeding was begun, and the fact that it was of value in alleviating the symptoms in 6 was in itself gratifying.

In 2 patients of the 8 who later died, an experiment was carried out to see what effect keeping the ulcerated bowel free from the irritation of ingested food would have on the symptoms. These patients both had severe pulmonary disease and intestinal disease of long standing, which had failed to respond to every therapeutic measure, including Pectin Agar. They had frequent loose, often bloody stools, marked tenesmus and frequent vomiting with almost constant abdominal pain. For five days they were given no food by mouth and received daily 3,200 cc. intravenously of a solution containing 10 per cent glucose and 5 per cent of a mixture of amino acids (Amigen, Mead Johnson and Company), yielding 1,920 calories. Although the diarrhoea was decreased, there was no decrease in the tenesmus, nausea and vomiting, and the abdominal pain seemed to be worse. This experiment is convincing evidence of the fact that the symptoms produced by the ulcerations are not improved by protecting the ulcers from the irritation of food residues. When these patients were fed Pablum and Pectin Agar, the abdominal distress was decreased.

We are not trying to indicate that Pectin Agar cures intestinal tuberculosis. In intestinal, as in pulmonary tuberculosis, it is the patient who, after all, gets himself well. It is recognized by all those who have made a pathological study of the disease that, as the pulmonary disease shows evidence of remission or permanent arrest, the ulcers in the intestines, whether treated or not, are probably also undergoing retrogressive changes and in many cases spontaneous healing. The 10 patients in our series who recovered from their intestinal disease all received active treatment in the form of pneumothorax, oleothorax or some surgical collapse procedure, and their pulmonary disease was in general improving. However, the added complication of intestinal tuberculosis with the resulting impaired nutrition made the outlook questionable in many cases. The condition of many patients with pulmonary tuberculosis seems to reach a stage of equilibrium between the processes of healing and of progression. At this critical stage, any complication may lead to progression of the disease. In the patient with healing pulmonary disease, this equilibrium may be disturbed unfavorably by the

added complication of intestinal involvement. By controlling the symptoms which interfere with adequate food intake, digestion and absorption, Pectin Agar aids in maintaining optimum conditions for recovery.

The end-results of our study appear less striking than those reported by McConkey (3), who states that 86 per cent of the cases receiving codliver oil and tomato juice were alive at the time of his report. It is very probable, however, that many of his patients had less advanced disease than those in our study, since 14 per cent of them had no symptoms referable to the intestines, the diagnosis being made entirely by X-ray. Many of our patients were obviously hopeless, but were given Pectin Agar to determine what could be accomplished in the way of relieving their symptoms. In a less extensive experience with codliver oil and tomato juice, we have been unable to demonstrate its striking effectiveness, either in alleviating the symptoms of the disease or preventing its progression. Steinbach and Rosenblatt (7), who made a careful examination of the necropsy material in 14 cases studied clinically, found little evidence of healing, and extensive fresh ulcerations despite prolonged vitamin therapy.

The mechanism by which Pectin Agar brings about relief of symptoms is as yet not completely determined. It very definitely allays hyperperistalsis, as evidenced by the decrease in stools and flatus. This return to a more physiological motility probably accounts for improvement in the symptoms of abdominal distress, distension, nausea and anorexia. The promptness with which relief is often secured makes it unlikely that healing of the ulcers, which is a slow process, is involved in recession of the symptoms.

CONCLUSIONS

1. In a group of 24 patients with secondary tuberculous enterocolitis, who were fed Pectin Agar with a low cellulose intestinal diet, recovery in a period varying from three months to one year occurred in 10. Eight of the patients died, 2 are improved and still under treatment and 4 left the hospital before the studies were completed.

2. Pectin Agar is of decided value in controlling the symptoms of intestinal tuberculosis. This results in an increased food intake with more normal digestion and absorption and gain in weight.

3. An adequate diet with optimum vitamin content is an essential factor in patients with tuberculosis. By restoring intestinal activity to a more physiological status, Pectin Agar favors the recovery not only of the intestinal disease, but of the accompanying pulmonary disease.

CONCLUSIONES

1. En un grupo de 24 enfermos que padecían de enterocolitis tuberculosa secundaria, y que recibieron Agar-Pectina con una alimentación pobre en celulosa, en 10 se obtuvo la reposición en un período que varió de tres meses a un año. Ocho de los enfermos murieron, 2 han mejorado y continúan en tratamiento, y 4 abandonaron el hospital antes de completar los estudios.

2. El Agar-Pectina posee valor decidido para cohibir los síntomas de la

tuberculosis intestinal, obteniendo un aumento de la ingestión alimenticia y una digestión y absorción más normales y aumento de peso.

3. En los tuberculosos un factor esencial consiste en una alimentación adecuada, con un contenido óptimo de vitaminas. Por devolver la actividad intestinal a un estado más fisiológico, el Agar-Pectina fomenta la reposición, no tan sólo de la afección intestinal, sino de la enfermedad pulmonar concomitante.

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TUBERCULOUS TRACHEOBRONCHITIS[1]

A Pathological Study

CHIA-SSU HUANG[2]

The pathology of tuberculous tracheobronchitis has been described earlier than a century ago (Carswell (4)). Its clinical significance was, however, not fully realized before the last decade. It is through the effort of many workers, among whom were Eloesser (6, 7, 8, 9, 10), Coryllos (5), Myerson (19, 20, 21), McConkey and Greenberg (16), Samson (27, 28, 29), Barnwell, Littig and Culp (2), Warren, Hammond and Tuttle (31), Epstein and Ornstein (11), Pierce and Curtzwiler (25) and Occhsli (23), that the symptomatology, roentgenographic appearance and bronchoscopic diagnosis were carefully worked out. With the full clinical recognition of the condition, the high mortality of the group of tuberculous patients with this complication and the lack of effective treatment for it, the incidence of the lesion and, particularly, its pathogenesis have renewed the interest of the pathologists as well as the clinicians.

In the University of Michigan Hospital, a study of the clinical records, protocols and tissue sections of all the cases of pulmonary tuberculosis coming to autopsy up to July, 1936 was made by Bugher, Littig and Culp (3) in 1937. In a series of 122 cases, involvement of some portion of the larynx, trachea or large bronchi was found in 59, or 48.4 per cent.

MATERIAL

This study is a continuation of that made by Bugher, Littig and Culp and consists of similar cases from the beginning of July, 1936 to the end of December, 1941, representing a period of five and a half years. There is, however, a minor difference in the selection of cases. In the earlier series, only the cases with tuberculosis as the primary cause of death were studied. In the period under the present study, there were 11 cases with definite active pulmonary tuberculosis, but the primary cause of death was a nontuberculous lesion (table 1). Among this group, there were tuberculous lesions in larynx and trachea in one each, and in large bronchi in 4. These cases were also included in the study. The only criterion for the selection of the cases in this series is, therefore, the presence of active pulmonary tuberculosis.

The tissue sections of all the cases were reviewed. The routine specimens consisted of from one to three sections of the larynx, trachea and large bronchi each, and more sections were prepared when gross lesions were present. Besides, 10 cases with extensive cavernous pulmonary tuberculosis but negative for any laryngo-tracheo-bronchial lesion were selected, and more sections of the larynx, trachea and bronchi were made from the specimens. Out of these 10 cases, one

[1] From the Section of Thoracic Surgery, Department of Surgery and the Department of Pathology, University of Michigan Medical School, Ann Arbor, Michigan.

[2] Fellow of Thoracic Surgery of the National Tsing-hua University, China.

was found to have tubercles in the submucosa of the larynx. For the determination of the prediction value of a single section, Bugher, Littig and Culp isolated the entire respiratory tracts from 8 fatal cases of pylmonary tuberculosis and 12 transverse serial blocks were made from each trachea. One section was prepared from each block and examined for evidence of tuberculosis. They came to the conclusion that, in fatal cases of pulmonary tuberculosis, the entire mucosa of the trachea or a large portion of it becomes involved practically simultaneously and a single section has a high prediction value. Nevertheless, one has to admit that the findings as obtained from this study represent only the lowest incidence of the laryngo-tracheobronchial lesion as the larynx, trachea and bronchus were each represented by one to three sections only.

TABLE 1

Autopsied cases having active pulmonary tuberculosis but their cause of death was a nontuberculous lesion

CAUSE OF DEATH	TUBERCULOUS INVOLVEMENT IN		
	Larynx	Trachea	Bronchi
Ruptured appendicitis	−	−	−
Toxaemia of pregnancy	−	−	−
Streptococcus septicaemia	−	+	−
Carcinoma of neck	+	−	−
Apoplexy	−	−	−
Anaesthesia for a bone operation	−	−	−
Suicide (hanging)	−	−	+
Septicaemia	−	−	+
Carcinoma of stomach	−	−	+
Bronchogenic carcinoma	−	−	+
Ruptured aneurysm	−	−	−

STATISTICAL STUDY

1. *General incidence of tuberculosis of the larynx, trachea and bronchi (table 2):* In a series of 115 autopsied cases with active pulmonary tuberculosis, there was involvement of some portion of the larynx, trachea or large bronchi in 50.4 per cent.

2. *Distribution of the lesion in the various regions of the respiratory tract (table 3):* In the group of 90 cases without laryngeal involvement, there was tuberculosis of trachea or bronchi or both in 33 cases, while 9 of the 25 cases with tuberculous laryngitis were free from any lesion in the trachea or bronchi.

3. *Relation to the pathology of pulmonary lesions (table 4):* The pulmonary lesions are classified according to the presence or absence of open cavities at the time of autopsy. It is to be noted that the incidence of tuberculosis of the larynx, trachea and bronchi in the group with open cavities was three times as high as that without them.

4. *Relation to extrapulmonary tuberculosis (tables 5 and 6):* Tuberculosis of the larynx, trachea and bronchi occurred in 9 of 15 cases without extrapulmonary

tuberculosis and 49 of 100 cases with it (table 5). Further analysis of the extrapulmonary lesions (table 6) revealed that intestinal tuberculosis was the most frequent condition irrespective of whether or not there was involvement of

TABLE 2

Incidence of tuberculosis of larynx, trachea and bronchi in 115 autopsied cases having active pulmonary tuberculosis

REGIONS	NUMBER OF CASES	PER CENT
Larynx	25	21.7
Trachea	22	19.1
Bronchi	45	39.1
Trachea or bronchi or both	49	42.7
Larynx, trachea or bronchi or any combination of them	58	50.4

TABLE 3

Distribution of tuberculosis in larynx, trachea and bronchi in 115 autopsied cases having active pulmonary tuberculosis

LARYNX	TRACHEA	BRONCHI	NUMBER OF CASES	PER CENT
−	−	−	57	49.6
−	−	+	24	20.9
−	+	−	2	1.7
−	+	+	7	6.1
+	−	−	9	7.8
+	−	+	3	2.6
+	+	−	2	1.7
+	+	+	11	9.7

TABLE 4

Relation of tuberculosis of larynx, trachea and bronchi to the pathology of pulmonary lesions in 115 autopsied cases having active pulmonary tuberculosis

REGIONS	WITH OPEN CAVITIES (75 CASES)		WITHOUT OPEN CAVITIES (40 CASES)	
	Number of cases	Per cent	Number of cases	Per cent
Larynx	23	30.7	2	5.0
Trachea	20	26.7	2	5.0
Bronchi	39	52.0	6	15.0
Trachea or bronchi or both	42	56.0	7	17.5
Larynx, trachea or bronchi or any combination of them	49	65.1	9	22.5

other organs. In the group of cases without intestinal involvement, the incidence of tuberculosis of the larynx, trachea and bronchi was the lowest.

5. *Relation to positive sputum (table 7):* The clinical records of the 58 cases with tuberculosis of the larynx, trachea and bronchi were reviewed in regard to the

examination of sputum for tubercle bacilli. No such examination was done in 12, either because of the absence of sputum or because the patient was admitted

TABLE 5

Relation of tuberculosis of larynx, trachea and bronchi to extrapulmonary tuberculosis in 115 autopsied cases having active pulmonary tuberculosis

REGIONS	WITHOUT EXTRAPULMONARY TUBERCULOSIS (15 CASES)		WITH EXTRAPULMONARY TUBERCULOSIS (100 CASES)	
	Number of cases	Per cent	Number of cases	Per cent
Larynx	0	0.0	25	25.0
Trachea	2	13.3	20	20.0
Bronchi	9	60.0	37	37.0
Trachea or bronchi or both	9	60.0	40	40.0
Larynx, trachea or bronchi or any combination of them	9	60.0	49	49.0

TABLE 6

Relation of tuberculosis of larynx, trachea and bronchi to intestinal tuberculosis in 115 autopsied cases having active pulmonary tuberculosis

REGIONS	INTESTINAL TUBERCULOSIS ALONE (28 CASES)		INTESTINAL AND OTHER EXTRAPULMONARY TUBERCULOSIS (30 CASES)		EXTRAPULMONARY TUBERCULOSIS WITHOUT INTESTINAL TUBERCULOSIS (42 CASES)	
	Number of cases	Per cent	Number of cases	Per cent	Number of cases	Per cent
Larynx	10	35.7	13	43.3	2	4.8
Trachea	9	32.1	8	26.7	3	7.1
Bronchi	17	60.7	10	33.3	9	21.4
Trachea or bronchi or both	17	60.7	13	43.3	10	23.3
Larynx, trachea or bronchi or any combination of them	18	65.0	19	63.5	12	28.6

TABLE 7

Sputum examination in 58 cases having tuberculosis of larynx, trachea and bronchi

Sputum positive for tubercle bacilli on direct smear	32
Sputum positive for tubercle bacilli on concentration or on culture	3
Sputum negative for tubercle bacilli	7
Gastric content positive for tubercle bacilli	3
Gastric content negative for tubercle bacilli	1
No laboratory examination	12
Total	58

in such a late stage that time did not allow for doing so. Of the 7 cases with negative sputum, in only one was a culture made, while the rest had direct smear examinations only, usually from a single specimen.

6. *Histological study (table 8):* The tuberculous lesions were differentiated into ulcerated and nonulcerated types. The latter showed mainly discrete tubercles in the submucosa; occasionally diffuse tuberculous granulation tissue was seen. The difference between ulcerated and nonulcerated lesions is merely a matter of different stages of the same process. Not infrequently one saw that the epithelium covering a submucosal tubercle was so thin that ulceration was about to occur. About two-thirds of the lesions in this series were ulcerated.

TABLE 8

Histological study

REGIONS	ULCERATED LESIONS		NONULCERATED LESIONS	
	Number of cases	Per cent	Number of cases	Per cent
Larynx	19	76.0	6	24.0
Trachea	16	72.2	6	27.8
Bronchi	29	64.4	16	35.6

DISCUSSION

The incidence of tuberculosis of the larynx, trachea and bronchi among 115 autopsied cases with active pulmonary tuberculosis was 50.4 per cent and that of the trachea and bronchi 42.7 per cent. This finding is in agreement with the earlier series reported by Bugher, Littig and Culp of this hospital. Much lower values were, however, reported by others. Minkovsky (18) in 1929, in a collection of 2,379 autopsies with tuberculosis as the fundamental disease, found affection of the larynx in 19.0 per cent and that of the trachea in 11.5 per cent of cases. Flance and Wheeler (12) in 1939 detected only 8 cases of tuberculous tracheobronchitis out of a series of 285 autopsies of pulmonary tuberculosis. It has to be pointed out that in these two series the examinations were mainly macroscopical, although Flance and Wheeler confirmed their diagnosis by microscopical examinations of the tissue grossly suspected of being tuberculous. The incidence of tuberculous tracheobronchitis in the fatal cases with active pulmonary tuberculosis should not be confused with that in clinical pulmonary tuberculosis. Clinically, many cases of tuberculous tracheobronchitis do not present characteristic symptoms and, therefore, are not examined by bronchoscopy, and small ulcers and flat submucosal lesions may not be detectable through a bronchoscope. In the series of cases in which routine bronchoscopic examination was done in all patients having active pulmonary tuberculosis, the incidence varied between 10 to 15 per cent (Warren, Hammond and Tuttle (31), and McIndoe, Steele, Samson, Anderson and Leslie (17)). When bronchoscopy was performed only on cases of pulmonary tuberculosis because of suggestive symptoms, Warren, Hammond and Tuttle reported an incidence of 57.4 per cent in 108 cases and Myerson (22) 40 per cent in 572 cases.

In my series, tuberculosis was present in the larynx alone in 9 cases, the trachea alone in 2 and the bronchi alone in 24. It occurred in both larynx and trachea in

2, larynx and bronchi in 3 and trachea and bronchi in 7. In 11 cases, it was distributed in all three regions of the respiratory tract. This distribution speaks against the theory of Lederer's (15) that tuberculous tracheobronchitis is secondary to a laryngeal lesion, but rather that they are all independently secondary to pulmonary tuberculosis. The preponderance of the lesions in the bronchi gives further support for the assumption that they extend from the lungs.

Various theories have been advanced in explanation of the pathogenesis of tuberculous tracheobronchitis. Primary tuberculosis of the trachea and bronchi was reported by Hedinger (14), Hausemann (13) and Schmorl (30). It should be very rare, if existent at all. All cases in the present series were associated with active pulmonary tuberculosis. A careful review of the autopsy protocols of the period under study revealed that there were 636 cases of inactive tuberculosis in the lungs or tracheobronchial lymph nodes, and 17 cases of milliary or active extrapulmonary tuberculosis with no active lesion in the lungs. None had a tracheobronchial lesion.

Haematogeneous spreading from a primary focus in the lungs undoubtedly does exist, but it probably does not play a major rôle in this condition. This is evidenced by the fact that in the 72 cases with extensive extrapulmonary distribution of tuberculosis, the larynx, trachea and bronchi were involved in only 31, or 43.1 per cent, while in 43 cases without such distribution, the involvement was 27, or 62.8 per cent.

Direct extension of tuberculosis from tracheobronchial lymph nodes through the adventitia into the bronchus was suggested by Ornstein and Epstein (24). This theory cannot be supported by the present study for two reasons. First, among the 58 cases of tuberculosis of larynx, trachea and bronchi the tracheobronchial lymph nodes were tuberculous in 51 and uninvolved in 7. The presence of cases of tuberculous tracheobronchitis in the absence of tuberculosis of tracheobronchial lymph nodes certainly speaks against the theory that the mucosal lesions have their origin in the adjacent lymph nodes. Second, in the vast majority of cases the lesions were in the mucosa and submucosa, while the adventitia of the trachea and bronchi was free.

Extension by contiguity was maintained by Reichle and Frost (26). According to them, the infection is carried by the extracartilaginous mucous glands adjacent to the diseased lymphatics and lymph nodes. The fact that the extracartilaginous portion is diseased only in the far advanced lesions in my series does not speak for this theory.

There are a few outstanding facts in this study. First, the tracheobronchial involvement was most frequent in the cases with open cavities. Second, with few exceptions, the patients had sputum positive for tubercle bacilli. Third, among the extrapulmonary lesions, tuberculosis of the intestine, with or without involvement of other organs, was the commonest associated condition. In a total of 58 cases with intestinal tuberculosis, lesions of the larynx, trachea and bronchi occurred in 37, while in 42 cases without intestinal involvement, they occurred in only 12. The development of tuberculosis of the intestine in the presence of positive sputum can be explained in most cases by the swallowing of

sputum loaded with tubercle bacilli. If the sputum contains enough virulent tubercle bacilli to invade the intestinal mucosa, it is not unlikely that the mucosa of the respiratory tract will also be affected. From these facts, one seems justified to conclude, in agreement with Bugher, Littig and Culp and also Auerbach (1), that tuberculous tracheobronchitis is, in most cases, brought about by the invasion of the mucous membrane or mucous glands by tubercle bacilli directly from the cavernous lesions in the lungs.

There still exist, however, cases of tuberculosis of the larynx, trachea or bronchi without open cavities in the lungs, as evidenced by 9 cases of the present series. Moreover, it has been recognized clinically that tuberculous tracheobronchitis may be present with little clinical or roentgenological evidence of a pulmonary lesion (Barnwell, Littig and Culp (2) and Ornstein and Epstein (24)). The presence of tubercle bacilli in the sputum in cases of tuberculous tracheobronchitis does not necessarily mean that the tracheobronchial lesion was secondary to an open tuberculous lesion in the pulmonary parenchyma, for the tracheobronchial mucosal lesion may, in itself, be the cause of the positive sputum. The explanation of the pathogenesis of this small group of cases of tuberculous tracheobronchitis without open parenchymal lesions is as yet unknown.

As to the type of lesions of the respiratory tract, ulceration predominated the picture. This is expected when one deals with a series of fatal cases in which the resistance of the body to infection is at its minimum.

SUMMARY AND CONCLUSION

A study of all the autopsied cases with active pulmonary tuberculosis admitted to the University of Michigan Hospital from July, 1936 to December, 1941, covering a period of five and a half years, revealed that tuberculous tracheobronchitis was present in 42.7 per cent of 115 cases, and when the laryngeal lesions were added, the incidence was 50.4 per cent.

The distribution of the cases with respect to the various combinations of lesions in the larynx, trachea and bronchi demonstrated no causal relationship between them. They are probably all secondary to pulmonary tuberculosis.

Direct implantation of tubercle bacilli from open cavities of the lungs to the mucous membrane or mucous glands seems to be the most plausible explanation for most of the cases.

Tuberculous ulceration is the predominating lesion of the respiratory tract in fatal cases.

SUMARIO Y CONCLUSIONES

En estudio de todos los casos (115) autopsiados con tuberculosis pulmonar activa que ingresaron en el Hospital de la Universidad de Míchigan de julio, 1936 a diciembre, 1941, o sea en cinco años y medio, reveló que había tráqueobronquitis tuberculosa en 42.7 por ciento, y agregando las lesiones laríngeas, en 50.4 por ciento.

La distribución de los casos con respecto a las varias combinaciones de lesiones

laríngeas, traqueales y bronquiales no reveló relación etiológica entre ellas, siendo probablemente todas secundarias a la tuberculosis pulmonar.

En la mayoría de los casos la explicación más plausible parece consistir en el implante directo de bacilos tuberculosos procedentes de cavernas pulmonares en la mucosa o glandulos mucosos.

En los casos letales la ulceración tuberculosa constituye la lesión predominante del aparato respiratorio.

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QUANTITATIVE ASPECTS OF SPECIFIC TUBERCULO-IMMUNITY[1,2]

H. J. CORPER AND MAURICE L. COHN

In no disease are the relative amounts of interacting factors of more decisive significance than they are in tuberculosis; and yet no exact scientific measure of the interacting relations of causative agent and host exists which can be applied readily in evaluating these factors in man. The significant biological reactions occur in an almost inaccessible bacillus and to a great extent in almost inaccessible host cells, where the results of natural disease in man are determined in one direction or the other. A predominant determinative factor here is specific tuberculo-immunity, which can only be approximated by reference to scientific animal experiment. In such experiments, the conditions can be adjusted by using an extremely wide infection range of bacilli, from as little as one-billionth to one milligram and, counterpoised against the bacilli, the specific immunity developed by vaccination over an almost equally wide range of vaccine. Thus it is readily understood why observers of five decades ago were able to note experimentally that a specific immunity existed at all (1). For this reason, Koch, Roemer, Calmette, Krause and others were encouraged by their studies. Even alert clinicians of former centuries had noted that "those who contracted pulmonary tuberculosis and took care of themselves might live a full life span," and it was no novelty to find advanced open cases continuing to live in spite of their tuberculous condition. Yet, even to the present time, there are those who believe in an increased specific susceptibility following a primary infection.

The discovery of avirulent mammalian tubercle bacilli by Calmette and their definition (2) opened the way for quantitative specific immunity studies in tuberculosis and it was found that there is a retardation of virulent tuberculous infection in animals resulting from a previous vaccination with viable avirulent human and bovine tubercle bacilli (3). Avirulent tubercle bacilli in amounts exceeding .001 mg. of fine suspension per cc. produce definite intracutaneous local lesions in man and animals similar to those resulting from the injection of the same nonviable tubercle bacilli. The extent of such local lesions in man and their slow retrogression would not seem to warrant the use of excessive amounts of these bacilli, as has been done in the past for producing immunity. Evaluation of the effects of various procedures upon tuberculosis in the guinea pig has usually been made on the basis of one or both of two criteria; first, the comparative extent of tuberculous involvement, giving no information on life expectancy, however; and second, and apparently of lesser value because of uncontrollable factors, the duration of life of the infected animals (4, 5). The life expectancy of guinea pigs infected subcutaneously or intravenously with highly virulent human tubercle bacilli is prolonged considerably by specific immunization and the type of tuberculosis likewise shows a transition to the more chronic favorable type. Specific immunity to tuberculosis was found to

[1] From the Research Department, National Jewish Hospital, Denver, Colorado.

[2] This study was aided by the Jacques Labarrere Fund for Tuberculosis Research.

persist almost unabated in its effects for at least two years. However, it is not consistently related to skin allergy or hypersensitiveness (the tuberculin reaction) since it persists when the skin reaction to reliable specific tests (tuberculin) is absent entirely, even after having been strongly positive in earlier tests in the same animal and to the same amount of tuberculoprotein.

SPECIFIC TUBERCULOSIS IMMUNITY PRODUCED WITH SMALL AMOUNTS OF VIABLE AVIRULENT HUMAN TUBERCLE BACILLI

In preliminary experiments aimed at noting whether small amounts of viable avirulent tubercle bacilli injected into guinea pigs would result in establishing a specific tuberculo-immunity as well as specific tuberculin allergy, a series of

TABLE 1

PRIMARY SUBCUTANEOUS TREATMENT	INTRACUTANEOUS TUBERCULIN REACTION	TUBERCULOUS INVOLVEMENT
Controls. Not vaccinated; infected only*	0	4***
	0	4
	0	3
	0	3
	0	4
1 mg. viable avirulent human tubercle bacilli two months prior to infection	3**	0
	3	0
	4	0
	4	0
	3	0
10^{-6} mg. viable avirulent human tubercle bacilli two months prior to infection	0	0
	1	0
	2	0
	1	0
	2	0

* 0.000,1 mg. of virulent human tubercle bacilli (H160) was used for infecting subcutaneously.

** The tuberculin reaction is graded from 0 = no reaction to 4 = a 2 cm. reaction with central necrosis.

*** The tuberculous involvement is graded from 0 = no macroscopic tuberculosis to 4 = a generalized massive disease of all the important organs.

guinea pigs was given a subcutaneous injection of a millionth of a milligram (0.000,001 mg.) of a fine suspension of avirulent human tubercle bacilli (about one month old). These animals were then infected subcutaneously with 0.000,1 mg. of a virulent strain of human tubercle bacilli (H160) about two months after vaccination. From one to two weeks prior to infection, the animals were tested with tuberculin intracutaneously (0.000,5 mg. tuberculoprotein). The animals were then examined about two months after infection to determine the extent of the organic tuberculosis as compared with control animals which had not been vaccinated. The findings are recorded in table 1.

Although consistent specific immunity was developed in guinea pigs previously studied following the subcutaneous vaccination after one to three months, it was surprising to note that even after the subcutaneous injection of as little as 0.000,001 mg. of viable avirulent human tubercle bacilli a definitely demonstrable specific immunity to virulent infection had developed in the vaccinated animals as gauged by pathologic-anatomical involvement. Although a positive tuberculin test was obtained in many of these animals following vaccination with such small vaccinating amounts of bacilli, certain animals gave no reaction but presented a definite specific immunity.

TABLE 2

The survival time of guinea pigs vaccinated with small amounts of avirulent human tubercle bacilli

VACCINATED SUBCUTANEOUSLY ONE MONTH PRIOR TO INFECTION	SURVIVAL TIME AFTER INFECTION IN DAYS	AMOUNT OF TUBERCULOSIS	AVERAGE SURVIVAL TIME AFTER INFECTION IN DAYS
Controls. Infected only	115	4*	134
	123	4	
	132	4	
	134	4	
	164	4	
1 mg. avirulent human tubercle bacilli	286	4	344
	340	4	
	344	4	
	374	3	
	375	4	
10^{-6} mg. avirulent human tubercle bacilli	147	4	197
	161	4	
	192	4	
	206	4	
	277	3	

* The amount of tuberculosis is graded from 0 = no visible macroscopic tuberculosis to 4 = a generalized disease involving all the important organs.

In order to ascertain the effect of these small vaccinating injections on the duration of life of the guinea pigs, another experiment (recorded in table 2) was planned in which the animals were vaccinated subcutaneously with 0.000,001 mg. of avirulent human tubercle bacilli. For comparison, another set was vaccinated with 1.0 mg. of avirulent human tubercle bacilli. Both sets were then infected subcutaneously one month after vaccination and controls were also given 0.000,001 mg. of virulent human tubercle bacilli (№ 160) subcutaneously. All the animals were then uniformly fed and handled to avoid extraneous deaths and the duration of life noted with the results tabulated.

It is evident from the results recorded in table 2 on the survival time of the vaccinated guinea pigs, compared with the controls which were infected only,

that the guinea pigs that had received a previous single subcutaneous injection of 0.000,001 mg. of avirulent human tubercle bacilli lived decidedly longer, an average of one hundred and ninety-seven days, as compared with an average of one hundred and thirty-four days for the controls. However, when compared with the animals vaccinated subcutaneously with the larger optimum amount of 1 mg. of avirulent human tubercle bacilli one month prior to infection, the latter survived a much longer average time (three hundred and forty-four days). The type of tuberculosis found at death, though advanced in the immune guinea pigs, was of the more regressive chronic healing type in these animals, as compared with that found in the infected controls.

As a result of the foregoing and numerous other experiments on the quantitative aspects of specific tuberculo-immunity, there appears to be a definite relationship between the amount of viable avirulent tubercle bacilli used for a single subcutaneous vaccination and the degree of specific immunity developed against virulent infection. Although this is not shown strikingly when the time intervals of examination remain fixed at a few months after the infection and the pathologic-anatomical tuberculous involvement is used as a gauge, since at this time in most cases negative findings attain in the specific immune animals. The effect of the specific immunity becomes more striking when the animals are permitted to succumb to the infection. Then the prolongation of life of the vaccinated animals is strikingly increased and the consequent disease is of a far less progressive and destructive type, as compared with the controls infected only with highly virulent tubercle bacilli. However, thus far no evidence was presented to discern whether repeated injections of small amounts of viable avirulent tubercle bacilli might not achieve equally good specific immunization to that found with a single large injection. To test this, the large amount of 1 mg. appeared to possess advantages for comparison, because of its optimum action, with the small amounts of 0.000,001 mg. repeated at definite intervals.

In the following experiment, a series of guinea pigs was vaccinated with 0.000,001 mg. of viable avirulent human tubercle bacilli given subcutaneously at intervals of two to three days to a total of ten injections. As comparison control, another series was given a single subcutaneous injection of 1 mg. of the same avirulent bacilli when the last vaccination injection was given to the foregoing series. One month later, these guinea pigs and an additional series of infection controls, infected only, were given a subcutaneous injection of 0.001 mg. of highly virulent human tubercle bacilli (H160). The controls were permitted to die from the disease, and half of the specific immunized series was killed at this time and examined for the amount of tuberculous involvement, while the remaining half of the guinea pigs in the two immune series was permitted to die naturally. The findings in this experiment are recorded in table 3.

The findings recorded in table 3 again verify the striking protective value of preventive vaccination with viable avirulent human tubercle bacilli. They did not indicate, however, that repeated very small injections (0.000,001 mg. totaling 0.000,01 mg.) of bacilli would attain the protective efficiency of a single large optimal subcutaneous injection (1 mg.) of the viable avirulent bacilli, gauging

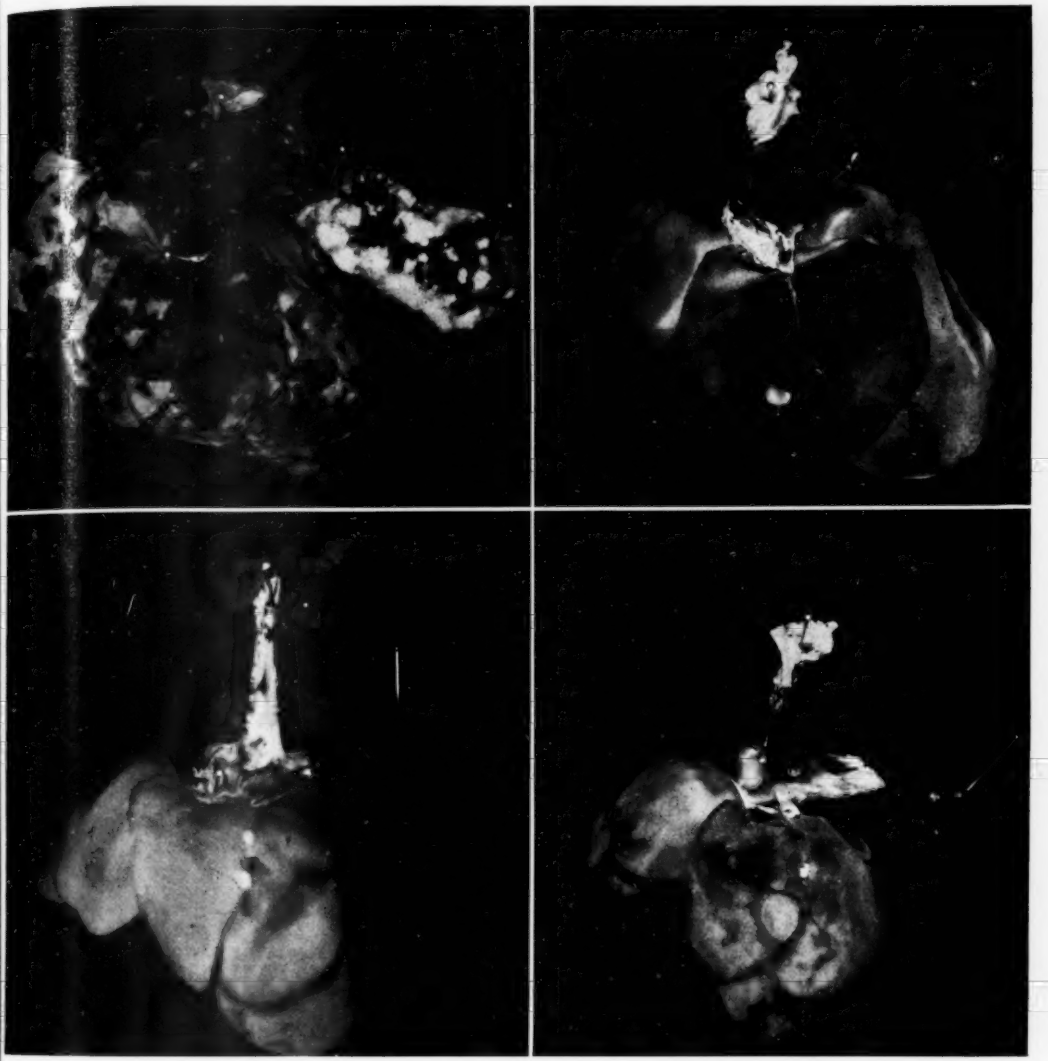

FIG. 1. Relative specific tuberculo-immunity

A. Upper left. Tuberculosis of a control guinea pig which died seventy-two days after subcutaneous infection with 0.001 mg. of highly virulent human tubercle bacilli (H160). Note massive generalized disease.

B. Upper right. Absence of organic tuberculosis in an immune control guinea pig vaccinated with 1 mg. of viable avirulent human tubercle bacilli one month prior to subcutaneous infection with 0.001 mg. of highly virulent human tubercle bacilli (H160), similar to infection control. The animal was killed seventy-two days after virulent infection.

C. Lower left. Similar to B except that the animal was vaccinated one month prior to virulent infection by giving 0.000,001 mg. of viable avirulent human tubercle bacilli subcutaneously. Note marked retardation of virulant infection by small vaccination at this time, seventy-four days after virulent infection.

D. Lower right. Similar to B except that this animal was vaccinated repeatedly (three times a week for 10 injections of 0.000,001 mg. viable avirulent human tubercle bacilli) and infected with virulent human tubercle bacilli one month after the last small vaccinating injection. Note marked retardation of disease by vaccination (several tubercles in spleen). The multiple small injections at these intervals for vaccinating did not appear to improve the specific immunity correspondingly.

the results both by the anatomical tuberculous involvement at the seventy-fourth day interval and by the prolongation of life of the experimental animal. Summation of effect from repeated injections appears to be evident, but it does not appear to accentuate the effect far beyond or even approaching that attained

TABLE 3

Relative specific tuberculo-immunity produced by repeated injections of small amounts of avirulent tubercle bacilli

VACCINATION	TUBERCULIN REACTION*	DAYS AFTER INFECTION WHEN THE ANIMALS DIED (D) OR WERE KILLED (K)	AVERAGE SURVIVAL TIME	TUBERCULOUS INVOLVEMENT
Control. Infected only; 0.001 mg. virulent human tubercle bacilli	0	D 61	67	4
	0	D 66		4
	0	D 68		4
	0	D 68		3
	0	D 72		4
1 mg. avirulent human tubercle bacilli subcutaneously one month prior to virulent infection	4	K 74		1
	2	K 74		1
	3	K 74		0
	3	K 74		0
	3	K 74		0
	3	D 182	251	4
	3	D 196		4
	3	D 246		4
	2	D 263		4
	3	K 370**		4
10 repeated subcutaneous injections at two to three-day intervals of 10^{-6} mg. avirulent human tubercle bacilli	3	K 74		1
	1	K 74		3
	1	K 74		0
	1	K 74		1
	3	K 74		1
	1	D 98	150	0***
	1	D 106		4
	2	D 167		4
	2	D 176		4
	2	D 205		4

* The tuberculin test was performed two days before virulent infection and about one month after last vaccination.

** This guinea pig was killed at three hundred and seventy days to terminate experiment.

*** This animal died free from tuberculosis, of extraneous causes.

by a single injection of an optimal amount of viable avirulent tubercle bacilli. The effect appears to be tempered primarily by the total amount of immune antigenic material used and, as was shown previously, even the tuberculo-allergic sensitizing effect can be differentiated from this definitely (6), both quantitatively and qualitatively.

Since the finer definitions of the immune reactions would appear to be elicited when using small amounts of antigen, it seemed desirable to determine the effects on specific immunity production resulting from the use of 0.000,001 mg. of viable avirulent human tubercle bacilli, subcultured for a long time on whole-egg medium containing broth, and the same medium without broth, a routine used in our laboratory for perpetuating cultures. The results of this study are recorded in table 4.

The findings recorded in table 4 indicate that the avirulent human tubercle bacilli subcultured on water-whole-egg medium lose some of their specific immunizing property when tested in small amounts (as little as 0.000,001 mg. of

TABLE 4

The effect of the addition of broth to egg medium for perpetuating avirulent human tubercle bacilli on the specific immunizing property

IMMUNIZING INJECTION	SKIN TUBERCULIN REACTION	SURVIVAL TIME AFTER INFECTION IN DAYS	AMOUNT OF TUBERCULOSIS	AVERAGE SURVIVAL TIME AFTER INFECTION IN DAYS
Control infected subcutaneously with 10^{-6} mg. virulent human tubercle bacilli (H160)	0	110	4	158
	0	141	4	
	0	156	4	
	0	159	4	
	0	226	3	
Injected subcutaneously one month prior to infection with 10^{-6} mg. avirulent human tubercle bacilli from whole egg medium	0	101	4	171
	0	171	4	
	0	181	4	
	0	190	4	
	0	213	3	
Injected subcutaneously one month prior to infection with 10^{-6} mg. avirulent human tubercle bacilli from broth whole egg medium	1	228	4	262
	1	230	4	
	0	253	4	
	1	262	4	
	1	337	4	

bacilli) and in comparison with the same bacilli subcultured on broth-whole-egg medium. When large amounts of bacilli are used, such as 1 mg., these effects are not evident because the immunizing potency of these bacilli is so decided that small differences cannot be noted with these large amounts. This is being studied further, both as to quantitative effects and on a greater variety of media.

In previous reports (4), the persistence of the specific tuberculo-immunity was shown to be unabated for as long as two years in guinea pigs when vaccinated with 1 mg. of avirulent human tubercle bacilli. In order to determine the effect of small vaccinations upon the persistence of specific immunity, guinea pigs were given 0.000,001 mg. of viable avirulent human tubercle bacilli and their resistance to virulent infection determined after six months and one year. The results are recorded in table 5.

The findings recorded in table 5 clearly demonstrate that specific immunity produced by vaccinating with small amounts (0.000,001 mg.) of viable avirulent human tubercle bacilli persists for over one year without appreciable diminution as determined by virulent infection and the survival time of the animals combined with the tuberculous involvement at time of death.

TABLE 5

Persistence of specific immunity following vaccination with small amounts of viable avirulent human tubercle bacilli

IMMUNIZING INJECTION	TIME AFTER IMMUNIZING INJECTION WHEN INFECTED	SURVIVAL TIME AFTER INFECTION IN DAYS	AMOUNT OF TUBERCULOSIS	AVERAGE SURVIVAL TIME AFTER INFECTION IN DAYS
Control, infected only—0.000,1 mg. virulent human tubercle bacilli H160	6 months	107	4	139
		110	3	
		118	4	
		140	4	
		218	3	
10^{-6} mg. avirulent human tubercle bacilli subcutaneously prior to infection		175	3	216
		178	4	
		190	4	
		247	4	
		289	4	
Control, infected only—0.000,1 mg. virulent human tubercle bacilli H160	1 year	60	4	94
		95	4	
		95	4	
		104	4	
		116	4	
10^{-6} mg. avirulent human tubercle bacilli subcutaneously prior to infection		146	3	223
		177	4	
		231	4	
		240	3	
		322	4	

SUMMARY

1. Specific tuberculosis immunity shows definite quantitative aspects as gauged by graded virulent infecting injections in guinea pigs and graded specific immunizing vaccinations with viable avirulent human tubercle bacilli. The criteria used were both the amount of anatomical tuberculous involvement at a definite interval and the duration of life following virulent infection. As little as 0.000,001 mg. of viable avirulent human tubercle bacilli incites a definitely demonstrable specific immunity to virulent infection though not as potent as when larger amounts (1.0 mg.) of bacilli are used for vaccinating. The pathological type of tuberculosis found at death is also perceptibly influenced favorably by these vaccinations with small amounts of bacilli.

2. When tested in small amounts, avirulent human tubercle bacilli cultured

on water-whole-egg media appear to be less efficient for specific immunization than when cultured on broth-whole-egg media. When large amounts of bacilli are used for immunization, this effect is not evident, because of the decided immunizing potency of these large amounts of bacilli, and small differences cannot be noted.

3. Specific immunity produced by vaccinating with small amounts (0.000,001 mg.) of viable avirulent human tubercle bacilli persists for over one year without apparent diminution in guinea pigs.

SUMARIO

1. La inmunidad específica a la tuberculosis revela aspectos cuantitativos bien definidos cuando se justiprecia por medio de inyecciones infectantes virulentas graduadas en el cobayo y vacunaciones inmunizantes específicas graduadas con bacilos tuberculosos humanos avirulentos viables. Las pautas tomadas fueron, tanto la extensión anatómica de la invasión tuberculosa en un plazo bien definido como la duración de la vida después de una infección virulenta. Hasta una cantidad ínfima, como 0.000,001 mg., de bacilos tuberculosos humanos avirulentos viables provoca una inmunidad específica claramente demostrable a la infección virulenta, aunque no tan potente como cuando se utilizan para la vacunación cantidades mayores (1.0 mg.) de bacilos. El tipo patológico de la tuberculosis descubierta en la muerte también se ve perceptiblemente afectada en sentido favorable por esas vacunaciones con pequeñas dosis de bacilos.

2. Cuando se comprueban en cantidades pequeñas, los bacilos tuberculosos humanos avirulentos, cultivados en medios de huevo íntegro y agua, parecen ser menos eficaces para la inmunización específica que los cultivados en medios de huevo íntegro y caldo. Cuando se toman para inmunización cantidades grandes, ese efecto no es manifiesto, debido a que la decidida potencia inmunizante de dichas grandes cantidades no permite observar pequeñas diferencias.

3. La inmunidad específica producida al vacunar con pequeñas cantidades (0.000,001 mg.) de bacilos tuberculosos humanos avirulentos viables dura más de un año sin aparente disminución en los cobayos.

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EFFECT OF DIET LOW IN THIAMINE AND RIBOFLAVIN ON AVIAN TUBERCULOSIS IN RATS [1]

GEORGE M. HIGGINS AND WILLIAM H. FELDMAN

The white rat has a relatively high resistance to experimental tuberculosis. This has been demonstrated by several investigators (1, 2). However, when rats are infected with virulent strains of tubercle bacilli, lesions will develop in the lungs, liver, spleen and lymph nodes but the rats rarely die of the disease. Some efficient humoral or cellular mechanism has been established during the phylogenetic development of this animal, assuring a relative immunity to tubercle bacilli. Wessels, in a recent study of experimental tuberculosis in the rat, expressed the belief that it is "possible that the native immunity of the rat is at least in part due to the failure of the development of cell necrosis or caseation."[2] He confirmed previous observations by others that the rat may not become sensitized to the tubercle bacillus or its protein derivatives as are the more susceptible rabbit and the guinea pig.

Since an adequate diet is essential to the inhibition of many pathological processes we believed it of interest to study experimental tuberculosis in rats which were fed a diet known to be inadequate with respect to certain fractions of the vitamin-B complex. Since, as Wessels stated, the mononuclear cells of the tuberculous lesion in the rat do not necrose, and since these cells may harbor excessive numbers of tubercle bacilli without apparent injury to them, may not this protection be due to a highly organized oxidative process within the cells operating by means of an effective enzyme system?

Recent extensive surveys of foods purchased for human consumption by families residing in our more highly organized industrial districts have shown that large numbers of our people are consuming relatively poor diets. These diets have been found to be unusually low in some of the fractions of the vitamin-B complex. Because of the national interest in an adequate dietary we believed it of interest to study the course of tuberculosis in animals which ate a human diet like that consumed by so many American families. Accordingly a diet consisting of foods commonly eaten by American families (table 1) was prepared. The foods were selected and the diet was prepared for rat consumption by Drs. Ray Williams and Russell M. Wilder of the Mayo Clinic Staff. The moist constituents of the diet when thoroughly mixed weighed 1,088 g. but when dried in the dark at a temperature of 65°C. for rat consumption, the constituents weighed 490 g. The proportions of carbohydrate, protein and fat were similar to those found in American diets generally. The caloric value per gram of dried diet was essentially the same as for the standard ration (3.5 to 4.0 calories per gram). Vitamins A, C and D, ferrous sulfate and tricalcium phosphate were added to the human diet in adequate amounts. The dried diet was assayed

[1] From the Division of Experimental Medicine, Mayo Foundation, Rochester, Minnesota.

[2] This explanation fails to take into account the equally likely possibility that necrosis does not occur owing to innate factors of immunity or resistance.

by Dr. Harold Mason of our chemical laboratories for its thiamine and riboflavin contents. The method of Hennessy (3) was employed for the thiamine determinations, and that of Conner and Straub (4) for the riboflavin assay. The results of these assays are included in table 2.

TABLE 1

Composition of diet low in thiamine and riboflavin (human diet)

ARTICLE	GRAM	ARTICLE	GRAM
Bread (patent flour)	230	Butter	45
Beef roast	100	Apricots	30
Cake	50	Carrots	75
Cream	75	Gelatin	100
Jelly	20	Lettuce	30
Pineapple	80	Potatoes	75
Rice, puffed	15	Rice, polished	25
Sugar	50	Tomatoes	75
White flour	10	Tricalcium phosphate	0.6
Ferrous sulfate	0.2	Iodized salt	2.0
Vitamin A	5,000 I.U.	Vitamin C	80 mg.

Vitamin D—500 I.U.
Moist weight 1,088 g.
Air dried at 65°C. to 490 g.

TABLE 2

Thiamine and riboflavin contents of the diets

	HUMAN DIET (TABLE 1)	STANDARD LABORATORY DIET
Thiamine, micrograms per gram	0.96	1.90
Riboflavin, micrograms per gram	2.00	7.50
Calories, per gram dry diet	3.0 to 4.0	3.5 to 4.0

METHODS

Twenty male rats all of the same age and same genetic strain (Wistar) were selected for this study. All rats were fed our standard laboratory ration until they had attained a weight of 80 g. Ten of them were then placed on the so-called human diet (table 1) and 10 of them continued to eat the standard ration. Eight weeks later, when the rats were four months old, each was inoculated intravenously with avian tubercle bacilli. The tubercle bacilli had been isolated one month previously from a pooled suspension of morbid tissues from the liver and spleen of a chicken that had naturally acquired tuberculosis. The dose of the inoculum per rat was calculated on the basis of 0.1 mg. of tubercle bacilli per 150 g. of body weight.

Smears were made of samples of heart blood of all animals twenty-four, forty-eight, seventy-two and ninety-six hours after inoculation. These were stained by May-Grünwald-Giemsa technique and differential counts were made.

Six months after inoculation, near the end of the experiment, the blood of all rats was again examined. Samples of blood were taken from the heart. Total erythrocyte and

total leucocyte counts were made, using pipets approved by the U. S. Bureau of Standards. Haematocrit determinations were made with the Van Allen haematocrit tubes and volumes of the erythrocytes in cubic micra were determined. Determinations of haemoglobin, in grams of haemoglobin per 100 cc. of blood, were made with the Cenco-Sheard-Sanford photelometer, using 0.1 cc. of blood diluted in 20 cc. of a 0.1 per cent solution of sodium bicarbonate. Two smears were made of each sample of blood. One was stained with brilliant-cresyl-blue, which stains reticulocytes and the other with the May-Grünwald-Giemsa technique. Differential counts of the leucocytes were made.

One hundred and eighty-four days after infection the surviving animals were killed for necropsy. At the time of necropsy the spleens were handled aseptically and a weighed amount of the spleen of each rat was ground and suspended in sufficient physiological solution of sodium chloride so that 1 cc. of the tissue suspension represented 100 mg. of the original splenic tissue; 1 cc. of each splenic suspension was cultured to attempt the demonstration of viable tubercle bacilli.[3]

At the time of necropsy a careful search was made for gross signs of tuberculous infection and tissues from lungs, liver, spleen, kidneys, testes and prostate were preserved for subsequent histological examination.

RESULTS

At the time the experiment was terminated, 17 of the 20 animals were still living. The animals that had died were in the group which were fed the human diet low in thiamine and riboflavin. Death had occurred within a few weeks after the animals had received the infective inoculum.[4]

The animals in both groups were in good physical condition. Those eating the standard ration had increased an average of 130 g., and those eating the human diet had increased an average of 93 g. Signs of vitamin deficiencies did not appear in any animal. Lesions of the skin, such as generalized dermatitis or acrodynia of paws or tails, which develop in animals on synthetic diets when the vitamin-B fractions are low, did not develop in these animals. Bloody nasal discharges or scaly encrustations on tips of ears likewise did not appear.

Although, at the end of the experiment, the animals in the two groups were strikingly dissimilar in their size and weight, the ability of the rats in both groups to exert, against the tuberculous infection, a fairly effective inhibitory mechanism was clearly evident. Without exception each of the 17 rats was tuberculous, and in every animal lesions characteristic of tuberculosis were demonstrated in lungs, liver and spleen. In 3 instances (animals on deficient human diet) the kidneys were tuberculous, although lesions did not occur in any testis. In another instance a large region of tuberculous involvement occurred in the midst of the seminal vesicles. In 5 rats (4 of which had received the adequate diet) extensive caseous tuberculous abscesses occurred in the paraprostatic tissues. The parenchymal structures of the gland were not involved

[3] The procedure followed in making the cultures required that the tissue suspension be treated with an equal amount of 5 per cent solution of oxalic acid. After subsequent washing and centrifugation the material was spread over the surface of four slants of egg yolk-agar medium containing 3 per cent glycerin. Incubation was at 37.5°C.

[4] Owing to inadvertency none of the 3 rats that died during the period of observation were examined at necropsy.

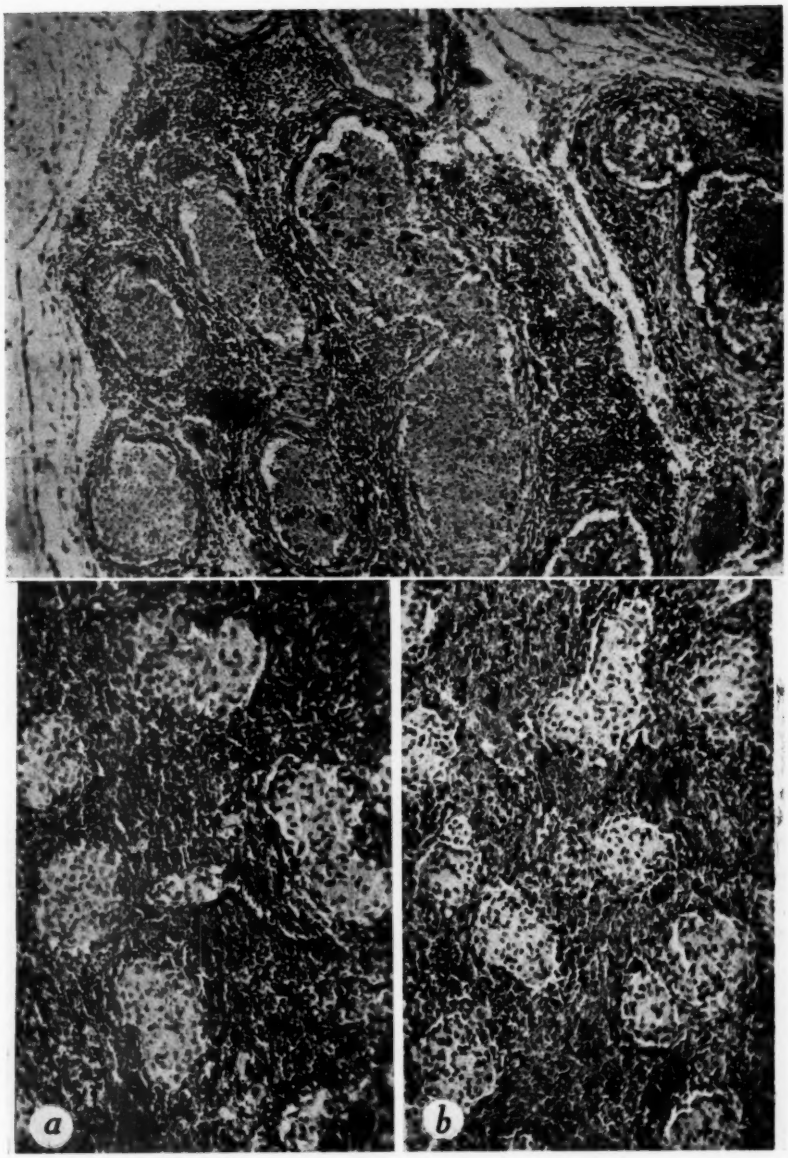

FIG. 1. (Top row.) Multiple paraprostatic tuberculous lesions, one hundred and eighty-four days after intravenous inoculation with avian tubercle bacilli. The small discrete basophilic foci are suggestive of the deposition of calcium. Rat maintained on standard laboratory ration (×63).

FIG. 2*a*. (Bottom row, left.) Numerous small, "hard," epithelial nodules in the pulp tissues of the spleen; one hundred and eighty-four days after intravenous inoculation with avian tubercle bacilli. Rat maintained on standard laboratory ration (×100).

FIG. 2*b*. (Bottom row, right.) Similar tuberculous lesions in spleen of rat maintained on a deficient ration and killed one hundred and eighty-four days after infection (×100).

(figure 1). A comparative study of the lesions occurring in the tissues of the two groups of animals failed to disclose any convincing differences in the severity of the morbid processes between the two groups of rats (figure 2).

The results of the attempts to isolate the infective agent from the respective spleens indicated that viable acid-fast bacillary forms were exceedingly numerous in splenic tissue. As mentioned previously, cultures were made from all of the spleens and in every instance innumerable, discrete bacterial colonies were obtained. Acid-fast bacillary forms were likewise demonstrated in abundance in sections of lesions of the other tissues.

While neither group of rats had convincingly less tuberculosis than the other, it was strikingly apparent that each rat, regardless of the diet it received, was tuberculous and harbored within its body many times more tubercle bacilli than would be necessary to initiate a progressive destructive disease in a less resistant aniamal. That a diet inadequate to provide for proper somatic growth and maintenance was without demonstrable effect in lessening the high natural resistance of the albino rat to tuberculosis prompts the suggestion that immunity and resistance to tuberculosis are factors not as easily manipulated as are factors constituting the more obvious physical attributes of animals. At least there was no evidence that a diet low in thiamine and riboflavin increased the severity of experimental avian tuberculosis for rats. Although the disease at the time of necropsy was wide-spread in its distribution, readily demonstrable in all of the animals and characterized by tubercle bacilli in excessive numbers, the infecting processes in the respective rats in most instances appeared to be rather well controlled. It appears likely that in these animals death as a consequence of tuberculosis would have been long deferred.

Changes of the blood: The data assembled from samples of blood taken from the heart of each animal just prior to infection with the organism show that there were no differences between the two groups of animals with respect to the morphological constituents of the bloods. Erythrocyte and haemoglobin levels were all within the normal range.

The differential percentage distribution of all leucocytes determined from samples of heart blood at twenty-four, forty-eight, seventy-two and ninety-six hours after infection indicated that some slight lymphocytosis had occurred in all rats of both groups during these first days following inoculation with tubercle bacilli. Since all animals showed the same trend in the elevation of the lymphocyte percentage, it seems clear that the low thiamine, low riboflavin human diet did not have any significant effect on this haemopoietic response to tuberculous infection.

As mentioned previously, just prior to the termination of the experiment the blood of all animals was again examined. Again there were no significant differences between these two groups of animals in respect to the blood findings. The mean erythrocyte and haemoglobin levels in the animals eating the human diet were appreciably higher than corresponding figures of animals eating the standard ration. However, this may be due to haemoconcentration, for animals eating the human diet weighed on the average 100 g. less than those eating the regular laboratory ration.

CONCLUSIONS

The results obtained indicated definitely that a diet significantly low in thiamine and in riboflavin did not influence in any recognizable manner the resistance of the white rat to experimental infection with avian tubercle bacilli. Whether or not the same results could be expected in rats infected with virulent mammalian tubercle bacilli is problematic.

CONCLUSIONES

Los resultados obtenidos indican definitivamente que una alimentación decididamente baja en tiamina y en riboflavina, no afectó en forma reconocible la resistencia de la rata a la infección experimental con bacilos tuberculosos. Está en tela de juicio si pueden o no esperarse los mismos resultados en las ratas infectadas con bacilos tuberculosos virulentos de mamífero.

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EXAMINATION OF POOLED SPUTUM SPECIMENS[1,2]

C. J. STRINGER AND H. E. COPE

This paper presents the results of animal inoculation and cultures of pooled seven-day sputum specimens from a selected group of patients in a medium-sized tuberculosis sanatorium. The study comprises the following types of patients:

1: Patients for diagnosis.
2: Patients on whom operative procedures were contemplated.
3: Patients previously operated.
4: Patients showing clinical and X-ray evidence of improvement and therefore demanding consideration for discharge.
5: Patients discharged from the sanatorium (follow-up observations).

In all instances the group was confined to individuals whose sputa were consistently negative for tubercle bacilli on direct smear.

METHODS

The first morning sputum was collected in sterile containers for seven consecutive days, the specimens being kept in the refrigerator until the entire series was completed. The single samples were then pooled. To each pooled specimen was added an equal volume of Hanks' solution (1). The mixture was shaken thoroughly and digested at 37°C. for thirty minutes. A volume of 2.5 per cent hydrochloric acid, sufficient to neutralize the excess alkali was then added, the mixture transferred to 50 cc. sterile centrifuge tubes and centrifuged at 2,000 r.p.m. for ten minutes. The supernatant fluid was decanted and duplicate smears prepared from the sediment. If acid-fast organisms were found in these smears no further examinations were made. If the examination of the stained slides was negative, the sediment was divided into two approximately equal parts, one of which was injected into the inguinal region of a guinea pig weighing from 250 to 300 g., and the second divided equally among four tubes of culture medium. Two of these tubes were Petragnani's and two Löwenstein's medium.

The guinea pigs were examined once a week for six weeks and then killed and autopsied. All animals dying before the end of the test period were also autopsied. All enlarged lymph nodes and abnormal tissues were removed, placed in sterile petri dishes and smears for acid-fast bacilli were prepared from the lesions. All abnormal tissues in which no acid-fast organisms were found or in which atypical acid-fast organisms were seen were fixed in formalin and examined histologically. The finding of acid-fast organisms of typical morphology in guinea pig lesions compatible with tuberculosis was considered a positive result.

[1] From the Ingham County Sanatorium and the Bureau of Laboratories, Michigan Department of Health, Lansing, Michigan.

[2] Read before the Michigan and Wisconsin Trudeau Societies at their joint meeting on Miscauna Island, June 12, 1942.

Following inoculation of the culture media, the cotton stoppers were thoroughly flamed, pushed down into the tubes, and the tubes covered with a celoceal cap. After about twenty-four hours the cap was immersed in melted paraffin, and two to three pin-sized holes pierced through the protective covering. Cultures were incubated at 37°C. and examined at weekly intervals until positive or until eight weeks had elapsed. The tubes were not opened unless colonies resembling *M. tuberculosis* were seen. Cultures were considered as positive only when bacterial morphology and staining and colonial characteristics met the commonly accepted criteria. If either was atypical, the organisms were injected into a guinea pig and pathogenicity demonstrated before classification as tubercle bacilli. These methods differed essentially from those of the Committee on Laboratory Procedures of the American Trudeau Society (2) only in the following particulars: (*1*) cultures were held only eight weeks, and (*2*) culture media was sterilized by autoclaving rather than inspissation.

RESULTS

In all, 1,147 examinations were made on 281 individuals with pulmonary tuberculosis; the stage of the disease is indicated in table 1. The distribution of patients parallels that of the average sanatorium population, 65, or about 25 per cent, being minimal, 108, or about 38 per cent, moderately advanced and the remainder (104, or about 38 per cent) far advanced. Variations in the average number of examinations per patient reflect largely relative diagnostic and therapeutic difficulties. Eighty examinations were listed as incomplete because either the animal died before the end of the test period and was negative, or because all cultures were contaminated. Of the total completed examinations, 453, or 41 per cent, were positive. We consider this particularly significant when it is realized that all these examinations were made on patients whose routine sputum examinations were negative.

Of the 453 positive examinations, 130 were positive on slide examination and 323 by pig or culture or both. Both pig and culture were positive in 149, the pig alone in 142, and the culture alone in 32 (table 2). If we had relied solely on guinea pig inoculation we would have missed 32 positive specimens. If cultures alone had been used we would have been wrong 142 times. The addition of cultures added about 3 per cent more positive findings.

These findings are at variance in respect to cultural results with both our own experience and that of many other investigators when examining urine or body-fluid specimens. During approximately the same period of time and using the same culture media, we examined 1,602 such specimens. Of these, 160 were positive by animal inoculation and 140 by culture. Pigs alone were positive in 30 of these examinations and cultures alone in 10.

An analysis on a percentage basis epitomizes the experience (table 3). Of the total examinations, 59 per cent were negative and 41 per cent positive by one or more of the procedures used. The 41 per cent positive results were made up of 11 per cent positive by slide examination, and 30 per cent by pig, culture or both. Twenty-seven per cent were positive by animal inoculation and 17 per

cent by culture. These gross figures are of interest, but the correlation with the amount of parenchymal involvement is of more importance. Although animal inoculation and cultural procedures increased the number of positive examina-

TABLE 1

The distribution of patients and the number and results of examinations in relation to the extent of pulmonary involvement

	EXTENT OF PULMONARY INVOLVEMENT						TOTALS
	1A	1B	2A	2B	3A	3B	
Number of patients	44	25	17	91	6	98	281
Number of examinations	120	135	51	345	27	460	1,147
Average number of examinations per patient	2.7	5.4	3.0	3.8	4.5	4.9	
Negative by all methods	92	79	33	187	17	206	614
Positive by slide examination	5	9	3	39	4	70	130
Positive by pig and/or culture	15	39	12	93	6	158	323
Incomplete examinations	8	8	3	26	0	35	80

TABLE 2

The number of positive guinea pig and cultural examinations in relation to the extent of pulmonary involvement

	EXTENT OF PULMONARY INVOLVEMENT						TOTALS
	1A	1B	2A	2B	3A	3B	
Positive pig and culture	6	15	2	38	2	86	149
Positive pig, negative culture	6	17	8	47	4	60	142
Positive culture, negative pig	3	7	2	8	0	12	32
Total positive pigs	12	32	10	85	6	146	291
Total positive cultures	9	22	4	46	2	98	181

TABLE 3

The results of examinations expressed in per cent in relation to the extent of pulmonary involvement

	EXTENT OF PULMONARY INVOLVEMENT						TOTALS
	1A	1B	2A	2B	3A	3B	
Negative by all methods	83.5	63.0	69.7	58.0	63.0	48.0	59.0
Positive by slide examination	4.5	7.0	6.3	12.0	15.0	16.0	11.0
Positive by pig or culture	13.0	30.0	24.0	30.0	22.0	36.0	30.0
Positive pig	10.7	25.0	21.0	27.0	22.0	34.0	27.0
Positive culture	8.0	18.0	8.0	14.0	8.0	23.0	17.0

tions in the group classified as minimal without symptoms by only 17 per cent, in the far advanced group with symptoms 52 per cent of the examinations were positive. The same increase in percentage of positive examinations with in-

creased severity of parenchymal involvement is seen in the break down of each of the three procedures used. The number positive by slide examination increased from 4.5 per cent in minimal lesions to 16 per cent for far advanced, or about four times. The number of positive pigs increased from 10.7 per cent in minimal disease to 34 per cent in far advanced, or three times, and the number of positive cultures from 8 per cent to 23 per cent, or again about three times.

So far we have discussed only results of examinations. When the application of these procedures is analyzed in terms of patients rather than examinations, the results become of more significance. It is to be noted that laboratory confirmation of diagnosis increased sharply when this three-pronged method of investigation was applied to persons having negative routine sputum examinations

TABLE 4

The results of examinations in relation to the reason for examination and the extent of pulmonary involvement, expressed in percentage

	POOLED SPUTUM SPECIMENS (SEVEN DAYS' COLLECTION)							
	Slide		Culture		Guinea pig		All methods	
	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative
I. Diagnosis (nature of infiltrations or presence of activity (246 patients))								
A. Minimal (75 patients)	13.3	86.7	16.9	83.1	38.5	61.5	49.3	50.7
B. Moderately advanced (65 patients)	23.1	76.9	42.0	58.0	72.0	28.0	83.1	16.9
C. Far advanced (106 patients)	55.7	44.3	55.3	44.7	93.6	6.4	98.1	1.9
II. Rejected for discharge (44 patients)			34.1	65.9	93.2	6.8		
III. Positive after discharge (34 patients)	8.8	91.2	29.0	71.0	96.8	3.2		

(table 4). In the group of patients with minimal lesions, tubercle bacilli were eventually demonstrated in almost 50 per cent of the patients; in the group with moderately advanced tuberculosis, organisms were found in 83 per cent of the patients; and in those with far advanced tuberculosis in 98 per cent. During the period of three years covering the collection of this series, there were 39 patients with moderately advanced and 45 with far advanced tuberculosis whose sputum was positive only by culture or guinea pig.

It has been our practice to advise additional periods of hospitalization for those patients whose sputum remained positive by any method. During the study period, 44 of the patients under consideration for discharge were retained in the sanatorium because of positive animal inoculation or culture.

If discharge had already been effected and the examination of the seven-day pooled sputum specimen was positive, the examination was repeated while the patient was still at home provided home conditions were optimal, and provided

there had been no other apparent change in the status of the tuberculosis. If repeated examinations remained consistently positive, the patient was readmitted to the sanatorium for further evaluation of the effectiveness of the program of treatment. In this out-patient group there were 34 persons exhibiting activity as measured by these procedures.

Table 5 presents the results of our experience with this laboratory method in measuring the efficacy of collapse therapy. In the last column it is noted that of the 254 cases treated by this method, 194 had positive and 60 negative sputa prior to collapse. The group with negative examinations includes largely patients with minimal infiltrations. Of the group of 176 patients with technically satisfactory collapse, only 15 had sputa which were positive on routine slide examination. Tubercle bacilli were found in the sediment of the pooled specimen from 4 more by slide examination, and from an additional 15 by animal inocula-

TABLE 5

The results of sputum examinations before collapse therapy, after technically satisfactory collapse and after collapse which is technically unsatisfactory

	SINGLE SPECIMEN SLIDE EXAMINATION		POOLED SPECIMEN						TOTAL	
			Slide examination		Culture		Guinea pig			
	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative
I. Pre-collapse (254 patients)	130	124	33	91	17	74	26	65	194	60
	51.2%	48.8%	26.6%	73.4%	18.7%	81.3%	28.6%	71.4%	76.4%	23.6%
II. Post-collapse										
A. Technically satisfactory (176 patients)	15	161	4	157	6	151	13	144	34	142
	8.5%	91.5%	2.5%	97.5%	3.8%	96.2%	8.3%	91.7%	19.3%	80.7%
B. Technically unsatisfactory (78 patients)	54	24	3	21	4	17	7	14	65	13
	69.2%	30.8%	12.5%	87.5%	19.0%	81.0%	33.0%	67.0%	83.3%	16.7%

tion or culture. There is no essential difference in the results obtained in the laboratory on the sputa from the untreated group and the group in which the collapse was technically unsatisfactory. This is more easily seen when the figures are expressed as percentages.

This type of laboratory study has often indicated the necessity for the review of cases whose treatment was thought to have resulted in sputum conversion but in whom tubercle bacilli were demonstrated by culture or animal inoculation methods. The conversion of a technically unsatisfactory collapse to a technically satisfactory one has often resulted in absolute sputum conversion. In others, bronchoscopy has revealed the presence of tracheobronchial tuberculosis. In a small proportion of the cases the collapse appeared to be technically satisfactory and no evidence of tracheobronchial tuberculosis could be demonstrated, though tubercle bacilli were found in the sputum, usually only intermittently.

SUMMARY

1. By animal inoculation and cultural examination of seven-day pooled sputum specimens, laboratory confirmation of diagnosis was accomplished in an

additional 50 to 98 per cent of the cases of tuberculosis negative by direct slide examination of single sputum specimens. The increase in positive results was in direct proportion to the extent of the disease and bore a direct relationship to the presence or absence of symptoms.

2. In this series guinea pig inoculation was more productive of positive findings than cultural methods in the proportion of 1.6 to 1, and than the slide examination of the pooled specimen in the proportion of 2.5 to 1. It was only by the use of all methods that maximum accuracy was obtained.

3. This laboratory method offers an efficient tool in measuring the effectiveness of collapse therapy, the advisability of discharge and for the control of discharged patients.

SUMARIO

1. Por medio de la inoculación en animales y de los exámenes culturales de esputos de 7 días combinados, se obtuvo la confirmación del diagnóstico en el laboratorio en un 50 a 98 por ciento más de los casos de tuberculosis que habían resultado negativos en los exámanes directos de las películas con ejemplares aislados de esputos. El aumento de la positividad estuvo en proporción directa con la extensión de la enfermedad y también en relación directa con la presencia o falta de síntomas.

2. En esta serie, la inoculación en el cobayo dió más resultados positivos que las técnicas de cultivo en la proporción de 1.6 a 1, y que el examen de las películas de los ejemplares combinados en la proporción de 2.5 a 1, pero el máximum de exactitud sólo se obtuvo cuando se utilizó una combinación de todos los métodos.

3. Esta técnica de laboratorio constituye un instrumento eficaz para justipreciar la eficacia de la colapsoterapia, la conveniencia del alta y para la fiscalización de los enfermos dados de alta.

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THE CHOLESTEROL CONTENT OF SPUTUM[1]

MAURICE BRUGER AND MILTON B. ROSENBLATT
With the technical assistance of Sylvia B. Ehrlich

Inflammatory diseases of the lungs produce bronchopulmonary necrosis, the extent of which varies with the severity of the process. As a result of tissue destruction, there is formed a highly cellular exudate in the respiratory passages. This exudate (sputum) acts as a bronchial irritant and is expelled by means of ciliary action, peristaltic movements and cough. Cholesterol, when found in the sputum, is probably derived from cellular autolysis. Theoretically, therefore, the quantitative determination of cholesterol in the sputum should serve as an index of the degree of bronchopulmonary destruction.

Although cholesterol has long been known to be a constituent of sputum (1, 2), the first extensive study of this subject was made by Kelly and Pinner (3) in 1928. The cholesterol was determined in dried sputum after extraction by chloroform in a Soxhlet apparatus. They found that the cholesterol content of the sputum averaged 8.75 mg. per gram of dried sputum in patients with active pulmonary tuberculosis with cavitation, 4.71 mg. in active pulmonary tuberculosis without cavitation, 4.67 mg. in patients with fibrotic pulmonary tuberculosis and 7.32 mg. in bronchiectasis. They concluded that the cholesterol content of the sputum has a rather definite though not constant relation to the type of pulmonary lesion.

Using a modified Babcock's tube, Cox (4) found the sputum of patients with pulmonary tuberculosis to be high in fat. He believed such determinations were of diagnostic and prognostic significance. Wells (5) maintained that the fat content of sputum was a measure of the number of pus corpuscles and the age of the pus, that is, the amount of fatty degeneration.

In the present study, the sputum of patients with various pulmonary diseases was analyzed for cholesterol by a simplified technique. It is hoped that the results obtained and the method devised will stimulate further work along these lines.

METHOD FOR THE DETERMINATION OF THE CHOLESTEROL CONTENT OF SPUTUM

Transfer 3 to 5 ml. of sputum to a 15 ml. pyrex centrifuge tube, utilizing the graduations on the tube for measuring purposes. Add an equal volume of a 3 per cent aqueous solution of sodium hydroxide and place the tube in a boiling water bath. When the mixture appears homogeneous (the clumps of sputum are hydrolyzed by the alkali in two to five minutes), remove the centrifuge tube from the water bath and set aside to cool. Pipette off 2 ml. of sputum digest and transfer slowly to a glass-stoppered centrifuge tube containing 12 ml. of a 3:1 alcohol-ether mixture (a glass-stoppered centrifuge tube is essential because the presence of alkali disintegrates rubber or cork). Place the tube on its side

[1] From the Medical Research Laboratory, Department of Medicine, New York Post-Graduate Medical School and Hospital, Columbia University; the Division of Pulmonary Diseases, Montefiore Hospital for Chronic Diseases; and the Second Medical Division, New York City Hospital.

for one to two hours (preferably overnight) in order to insure complete extraction of the cholesterol by the alcohol-ether mixture. Centrifugalize until satisfactory packing of the sediment is obtained. Pour off the supernatant fluid into a beaker of 50 ml. capacity. Evaporate the alcohol-ether extract to dryness in an incubator set at 60°C. Extract the sediment with two washings of 2 ml. each of chloroform and transfer the extracts to a 10 ml. glass-stoppered graduated cylinder. Make up to a volume of 5 ml. with chloroform and add 2 ml. of acetic anhydride and 0.1 ml. of concentrated sulphuric acid for the development of the Liebermann-Burchard color reaction. Standard solutions containing 0.5 mg. and 0.25 mg. of cholesterol in 5 ml. of chloroform are prepared simultaneously with acetic anhydride and sulphuric acid. Compare in a colorimeter the unknown with the appropriate standard solution.

Calculation:

$$\frac{R_s}{R_u} \times St \times 100 = \text{mg. of cholesterol in 100 ml. of sputum}$$

Where R_s = reading of standard
R_u = reading of unknown
and St = mg. cholesterol in 5 ml. of standard solution.

MATERIAL AND PROCEDURE

The present studies were carried out on 50 patients with various bronchopulmonary diseases grouped as follows: 25 with pulmonary tuberculosis, 10 with pulmonary malignancy and a miscellaneous group of 15 patients with bronchiectasis, abscesses, bronchopneumonia, lobar pneumonia, silicosis, bronchial asthma, hypertensive and arteriosclerotic heart disease with congestive failure. In each case, the clinical diagnosis was confirmed by bacteriological studies of the sputum, X-ray films, bronchoscopic examinations, biopsy specimens and, in the majority of instances, by postmortem examinations.

A twenty-four hour specimen of sputum was collected in a wide-mouthed bottle. Each patient was instructed to avoid contaminating the sputum, as far as possible, with saliva. In this way, the factor of salivary cholesterol (6) was minimized. Each specimen of sputum was divided into two aliquot portions and the cholesterol determined in each. This procedure was repeated invariably on the following day and, in some instances, on additional days. The values listed in the tables, therefore, represent an average of at least four determinations.

RESULTS

Table 1 shows the results obtained in 25 patients with pulmonary tuberculosis. Twenty of these had extensive bilateral fibrocaseous involvement with cavities and a sputum which was positive for acid-fast organisms. In this group, the cholesterol content of the sputum ranged from 12.3 to 106.4 mg. per 100 ml. but in only 2 of these were the values comparatively low (cases 4 and 8). In 18 of the 20 cases, the sputum contained more than 30 mg. of cholesterol per 100 ml. of sputum. In one patient with nodular miliary involvement, measurable quantities of cholesterol were not detected in the sputum (case 25). In 4 patients with arrested pulmonary tuberculosis, the cholesterol content of the sputum was 50.1 mg., faint trace, 0 and 15.5 mg. per 100 ml., respectively (cases 21, 22, 23 and 24).

Table 2 demonstrates the results obtained in 10 patients with pulmonary malignancy, 9 of whom had primary bronchogenic tumors and one a metastatic sarcoma. This latter patient also had an arrested tuberculous lesion. The cholesterol content of the sputum in this group ranged from 0 to 54 mg. per 100 ml. but in only 2 of those was it higher than 30 mg. per 100 ml. (cases 26 and 30).

TABLE 1

The cholesterol content of the sputum in patients with pulmonary tuberculosis

CASE NUMBER	AGE	SEX	CHOLESTEROL IN SPUTUM
Bilateral fibrocaseous cavitary—active or quiescent: tubercle bacilli present in sputum			
	years		*mg./100 ml.*
1	37	M	61.5
1	21	M	41.8
3	45	M	62.7
4	28	M	15.2
5	63	M	106.4
6	40	M	88.7
7	53	M	35.0
8	24	F	12.3
9	51	M	86.5
10	28	M	46.7
11	44	M	39.0
12	45	M	43.5
13	30	F	31.0
14	39	M	36.4
15	50	F	45.5
16	24	F	31.0
17	26	M	39.7
18	34	M	52.1
19	48	F	100.0
20	32	M	30.0
Bilateral fibrotic—arrested: no tubercle bacilli in sputum			
21	44	M	50.1
22	48	M	faint trace
23	23	F	0
Unilateral fibrotic—arrested: no tubercle bacilli in sputum			
24	40	F	15.5
Bilateral nodular miliary—active: tubercle bacilli present in sputum			
25	38	M	0

In 7 of the 10 patients, the cholesterol content of the sputum was less than 15 mg. per 100 ml.

Table 3 shows the results obtained in 15 patients with miscellaneous bronchopulmonary lesions. In patients with bronchiectasis, pulmonary abscess and suppurative bronchopneumonia, the cholesterol content of the sputum was high,

ranging from 19.6 to 79.8 mg. per 100 ml. In sharp contrast, the sputum of patients with silicosis, bronchial asthma and congestive heart failure did not contain measurable quantities of this sterol.

TABLE 2

The cholesterol content of the sputum in patients with pulmonary malignancy

CASE NUMBER	AGE	SEX	TYPE OF LESION	CHOLESTEROL IN SPUTUM
	years			*mg./100 ml.*
26	47	M	Adenocarcinoma	31.0
27	65	M	Adenocarcinoma	0
28	50	M	Squamous cell carcinoma	0
29	52	M	Squamous cell carcinoma	faint trace
30	76	M	Squamous cell carcinoma	54.0
31	65	M	Squamous cell carcinoma	0
32	44	M	Squamous cell carcinoma	23.2
33	68	M	Squamous cell carcinoma	11.5
34	60	M	Squamous cell carcinoma	14.8
35	49	M	Metastatic sarcoma	8.6

TABLE 3

The cholesterol content of the sputum in patients with various pulmonary diseases other than tuberculosis or malignancy

CASE NUMBER	AGE	SEX	TYPE OF LESION	CHOLESTEROL IN SPUTUM
	years			*mg./100 ml.*
36	54	M	Bronchiectasis	45.3
37	35	M	Bronchiectasis	54.9
38	50	M	Bronchiectasis	23.1
39	52	M	Abscess, acute, putrid	79.8
40	35	M	Abscess, chronic	19.6
41	19	M	Bronchopneumonia, suppurative	52.1
42	58	M	Bronchopneumonia, suppurative	45.2
43	24	M	Lobar pneumonia	21.0
44	44	M	Silicosis	0
45	42	M	Silicosis	0
46	22	F	Bronchial asthma	0
47	33	F	Bronchial asthma	0
48	57	M	Hypertensive heart disease with congestive failure	0
49	69	M	Hypertensive heart disease with congestive failure	0
50	71	M	Arteriosclerotic heart disease with congestive failure	faint trace

In one patient with suppurative bronchopneumonia (case 41), the cholesterol content of the sputum was followed during the various stages of his illness. During the early acute stages, all values exceeded 50 mg. per 100 ml. As the clinical status of the patient improved, the sputum cholesterol decreased. On

the eighteenth day of illness, the cholesterol content of the sputum was 18.1 mg. per 100 ml. and on the thirty-fourth day, just prior to discharge, cholesterol could not be detected in the sputum. In the second patient with suppurative bronchopneumonia (case 42), the cholesterol content of the sputum on the thirtieth day of illness was 45.2 mg. per 100 ml. Ten days later, clinical improvement was accompanied by a decrease in sputum cholesterol to 28.8 mg. per 100 ml.

TABLE 4

Correlation of repeated sputum cholesterol determinations at stated intervals in ten patients with chronic pulmonary disease

CASE NUMBER	PULMONARY LESION	CHOLESTEROL IN SPUTUM		INTERVAL BETWEEN DETERMINATIONS
		First determination	Second determination	
		mg./100 ml.	*mg./100 ml.*	*days*
1	Tuberculosis	63.5	59.5	10
2	Tuberculosis	49.0	38.2	10
3	Tuberculosis	71.6	51.2	10
4	Tuberculosis	16.7	14.5	10
6	Tuberculosis	97.4	84.4	10
8	Tuberculosis	12.0	12.5	75
21	Tuberculosis	42.2	54.1	10
29	Malignancy	faint trace	faint trace	60
30	Malignancy	44.5	58.8	50
36	Bronchiectasis	47.8	49.5	10

TABLE 5

Correlation of the cholesterol content of the sputum and of the blood in patients with pulmonary tuberculosis

CASE NUMBER	CHOLESTEROL IN SPUTUM	CHOLESTEROL IN BLOOD
	mg./100 ml.	*mg./100 ml.*
1	63.5	180
2	49.0	112
3	71.6	250
4	16.7	180
6	97.4	173
9	86.5	128
13	31.0	200
15	45.5	204
21	42.2	230
22	faint trace	247

Table 4 demonstrates repeated determinations of sputum cholesterol in patients with various chronic bronchopulmonary diseases in whom the disease process, as far as could be determined clinically, remained unchanged. The remarkable constancy of many of these determinations is well shown in spite of intervals of as long as seventy-five days between determinations and of marked differences in sputum volumes.

Table 5 attempts to correlate sputum and blood cholesterol determinations in 10 patients with pulmonary tuberculosis. No such correlation was observed.

COMMENT

When the present study was planned, it was assumed that patients with pulmonary malignancy would show excessive amounts of cholesterol in the sputum as compared to those with inflammatory disease of the lungs, since it is generally recognized that malignant tumors are rich in this sterol. This assumption failed to materialize; in fact, the reverse appeared to be the case. In 18 of 20 patients with bilateral fibrocaseous pulmonary tuberculosis with cavitation, the cholesterol content of the sputum exceeded 30 mg. per 100 cc.; in only 2 of 10 patients with primary bronchogenic tumors did the sputum cholesterol exceed this figure.

Of interest were the repeated observations that all forms of suppurative bronchopulmonary disease (tuberculosis, bronchiectasis, abscess, suppurative bronchopneumonia) were accompanied by high sputum cholesterols. In contrast, non-suppurative diseases (silicosis, bronchial asthma and congestive heart failure) were associated with little or no sputum cholesterol.

SUMMARY AND CONCLUSIONS

The cholesterol content of the sputum is an index of the degree of bronchopulmonary destruction. Further studies are necessary to evaluate the diagnostic and prognostic importance of such determinations. In view of the fact that suppuration may be a sequel of many pulmonary conditions, it is unlikely that the determination of cholesterol in the sputum will serve as an absolute diagnostic index. However, in conjunction with other clinical and laboratory data, it may prove exceedingly helpful in establishing the diagnosis. Furthermore, in patients with acute or subacute suppurative pulmonary disease, increasing or decreasing bronchopulmonary destruction may be gauged by the repeated analyses of the sputum for cholesterol. A comparatively simple technique for the determination of this sterol in sputum is described.

SUMARIO Y CONCLUSIONES

El contenido de colesterol en el esputo constituye un índice de la intensidad de la destrucción broncopulmonar, pero se necesitan más estudios para justipreciar la importancia diagnóstica y pronóstica de tales determinaciones. En vista de que la supuración puede ser una secuela de muchos estados pulmonares, es improbable que la determinación del colesterol en el esputo sirva como índice diagnóstico absoluto, aunque unida a otros datos clínicos y de laboratorio, puede resultar de mucho valor para establecer el diagnóstico. Además, en los enfermos de neumopatía supurada aguda o subaguda puede apreciarse el aumento o disminución de la destrucción broncopulmonar repitiendo los análisis del esputo en busca de colesterol. Descríbese una técnica comparativamente sencilla para determinar la presencia de dicho esterol en el esputo.

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CLINICAL NOTES

SCROTAL PNEUMOCELE[1]

A Complication of Pneumoperitoneum

RAYMOND W. MONTO AND HENRY A. BRADFORD

The successful use of pneumoperitoneum as an adjunct to collapse therapy in pulmonary tuberculosis has resulted in wider employment of this procedure. The technical difficulties encountered in this method are but slightly greater than those in performing a pneumothorax; complications are comparable. It is the purpose of this communication to report an unusual complication of pneumoperitoneum.

J. D., a white male age twenty-four, entered the Henry Ford Hospital complaining of having had haemoptyses for several days. Constitutional symptoms were not a feature. Except for lobar pneumonia in the right lower lung two years previously, the past history was negative. On examination, findings of note were limited to the chest. Impairment of percussion note was found at the right apex and the breath sounds in the same area were suppressed. The right side of the diaphragm showed moderate limitation in excursion. No other positive findings in reference to the chest were noted. In the examination of the abdomen it was observed that the inguinal rings were slightly relaxed. X-ray examination of the chest revealed extensive infiltration in the upper half of the right lung.

Attempts to induce pneumothorax on the right were unsuccessful. Phrenic crushing was performed resulting in paralysis of the right diaphragm. Only slight elevation of the diaphragm on this side resulted and pneumoperitoneum was employed as a means of producing better collapse.

The first intraperitoneal injection of 400 cc. of air was given in the left upper quadrant without difficulty. A second refill of 700 cc. was introduced the next day. Near the end of the procedure, the patient experienced a cramp-like pain in the left inguinal area. Several hours later examination showed the left side of the scrotum to have ballooned out to almost the size of a small grapefruit. Inspection revealed the left scrotum to be blown up with air; the left testicle was easily palpated at the bottom of the scrotal sac. The complication is illustrated in figure 1.

The following day the scrotum had decreased in size. A third air injection was carried out. During the insufflation of air the patient felt a "moving pain" in the region of the inguinal canal. Pressure over the left internal ring instantly stopped the distress. A pressure pad was applied over the ring and, following the procedure, was left in place. The patient was kept in a Fowler's position during the next four days. Subsequent refills were continued without incident.

DISCUSSION

The complications from the introduction of air into the peritonel cavity are numerous and of varying significance. Subcutaneous emphysema is frequently noted and offers no difficulty. Air embolism, a serious complication, has been encountered in pneumoperitoneum relatively more often than in pneumo-

[1] From the Department of Medicine, Henry Ford Hospital, Detroit, Michigan.

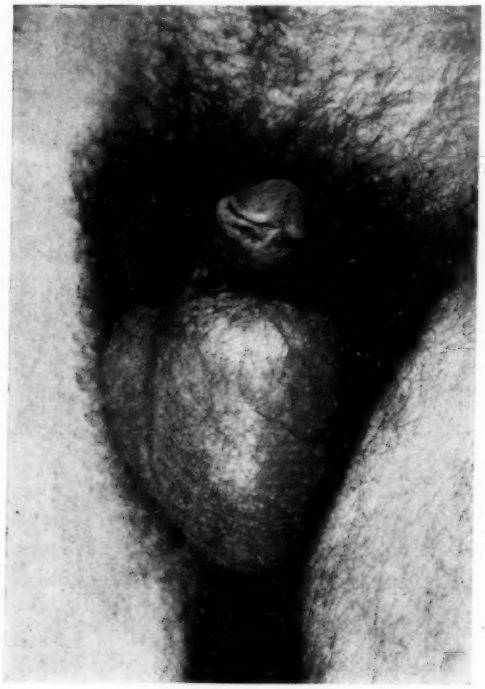

FIG. 1. Photograph of a patient receiving pneumoperitoneum, demonstrating scrotal pneumocele.

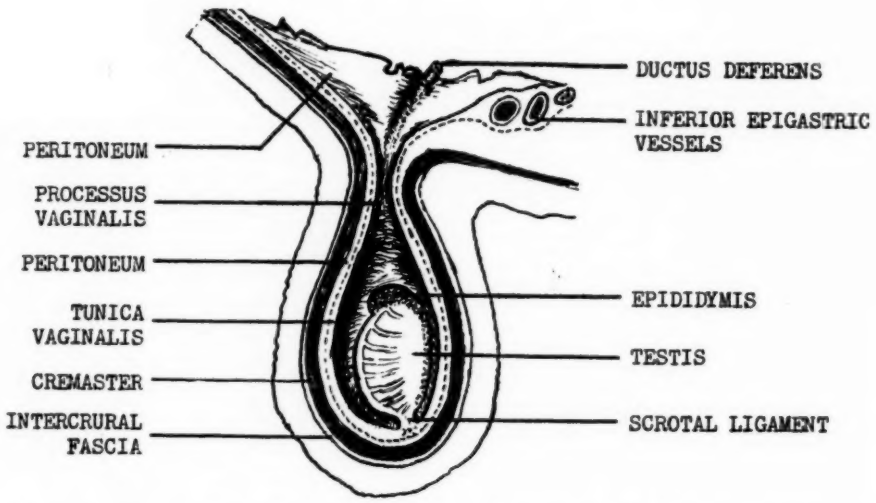

FIG. 2. Diagram showing relations of descended testicle to the *tunica vaginalis*. The upper portion of the *processus vaginalis* has remained in open communication with the abdominal cavity. Air passing through into the lower portion of the space caused balloon-like expansion of the scrotum with the testicle being held to the floor of the structure by the scrotal ligament. (After Piersol (1).)

thorax. Other accidents reported are: accidental pneumothorax, pneumomediastinum, enlargement of inguinal or umbilical hernia, diastasis of the abdominal rectus muscles, intraäbdominal pneumocele, peritoneal shock, ascites, dyspnoea, cyanosis, nausea and vomiting, and evidence of diaphragmatic irritation. Intraäbdominal haemorrhage and interestinal perforation are almost never seen by experienced operators. To the above list may be added scrotal pneumocele.

In the development of the male sex organs, the testes migrate from a retroperitoneal position downward into the scrotum in association with a pocket of peritoneum. Normally, in early months of childhood, the tubular evagination of peritoneum extending into the scrotum becomes closed. The pocket of peritoneum is termed the *processus vaginalis* and the occluded portion the *ligamentum vaginale*. Various anomalies do occur and occasionally there exists a passageway between the peritoneal cavity and *tunica vaginalis*. This anatomy presents the picture of potential hernia without demonstrable hernial sac. Circumstances indicate that the latter condition existed in the patient reported prior to pneumoperitoneum. A diagrammatic sketch of the anatomy involved is seen in figure 2.

Air within the peritoneal cavity has been observed to have an irritant effect and may well have resulted in final closure of the previously mentioned *processus vaginalis*. The pressure pad over the internal inguinal ring was subsequently removed and, despite continued refills with air and eventual increase in intraperitoneal pressures, no further air entered the scrotum.

SUMMARY

A complication of pneumoperitoneum, scrotal pneumocele, is reported. This condition was successfully combated so as not to prevent continuance of this form of treatment.

SUMARIO

Descríbese una complicación del neumoperitoneo: neumocele escrotal. El estado fué combatido con éxito a fin de no impedir la continuación de dicha terapéutica.

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METASTATIC ABSCESS OF THE BRAIN[1]

A Complication in a Patient with Pulmonary Tuberculosis

R. J. DANCEY

E. H., a white male engineer of thirty-seven years, was admitted to the Wisconsin State Sanatorium in May, 1939, his chief complaint being cough. Suggestive symptoms had been present as early as 1928, but a diagnosis of tuberculosis was not made until October, 1934, when he entered a sanatorium. During 1935 and 1936 he was treated with bilateral artificial pneumothorax. Because of spontaneous pneumothorax on the right and pleural effusion on the left, this form of treatment was abandoned. In March, 1939, extrapleural pneumothorax was established on the left at the Wisconsin General Hospital, from which institution he was transferred to the State Sanatorium.

The admission diagnosis was active, far advanced pulmonary tuberculosis, productive on the right, exudative on the left, with extrapleural pneumothorax on the left and atelectasis of patchy type in the left base.

The condition of the patient on admission was fair, with temperature ranging between 98.6° and 99.6°F., mild tachycardia, a vital capacity of 40 per cent and mild anaemia. It was observed that a high degree of suggestibility and apprehensiveness was present, with an unusual tendency to worry over trifles, but no other nervous or mental abnormalities were noted. A left phrenic crush was performed in October, 1939, because of persistently positive sputum, and as a prelude to thoracoplasty. The atelectasis in the left base continued to progress, and in May, 1940 thoracoplasty was performed on the left, which successfully closed the extrapleural space with the removal of four ribs, and for a short time was followed by a negative sputum. Effusion had occurred at times in the extrapleural space, but it was never purulent. Progression was noted on the right in October, 1940 and continued until the end. Haemoptysis became a troublesome symptom after February, 1941, and pneumoperitoneum was instituted in August of that year without benefit.

On October 5, 1941, there occurred a seizure of twenty minutes duration, during which the patient was semicomatose, and there was a slight tremor of the extremities. On October 7 he began to complain of right-sided headache. He became increasingly drowsy and on October 11 flaccidity of the right side of the face was observed. During the following week paresis and moderate rigidity of the left upper and lower extremities developed. Nuchal rigidity and Kernig's sign were not demonstrable. The patient was comatose for several days before his death, which occurred on October 17, 1941.

The temperature curve had been normal from shortly after admission until January, 1941. Thereafter it was constantly elevated between 98.6° and 100°F., with an acute febrile episode associated with pulmonary haemorrhage from August 3 to 8, when the temperature reached 103.4°F. On September 24 the

[1] From the Wisconsin State Sanatorium, Statesan, Wisconsin.

fever again became accentuated and remained in the neighborhood of 101°F. with occasional higher peaks and recessions until death.

At the time when the neurological symptoms became manifest, twelve days before death, the general status of the patient was so poor that diagnostic lumbar puncture was not thought justified. The clinical diagnosis was thought to rest between tuberculoma of the brain and tuberculous meningitis.

The necropsy findings of interest were as follows: The right pleural space was largely obliterated by thin fibrous adhesions. The apex of the right lung contained a few scattered small fibrocaseous nodules. The right lower lobe contained an area of fibro-atelectasis in its upper two centimeters, just below which appeared a cavity 2 cm. in diameter. This cavity contained yellow pus of moderately thick, homogeneous consistency. It had a fibrous wall with an irregular necrotic lining, giving the appearance of a typical tuberculous cavity. The remainder of the right lower lobe contained scattered fibrocaseous tubercles and nodules of diameters ranging from 1 mm. to 1 cm. There was mild basal bronchiectasis of cylindrical type.

The left pleural space was entirely obliterated, and the pleura was particularly dense over the apex, in the area of the former extrapleural pneumothorax pocket. The volume of the left lung was about one-third that of the right. The parenchyma of both lobes was largely replaced by multilocular cavities with ragged walls, containing brownish pus. The remaining parenchyma was airless, dark red and fibrous. The main bronchus was reduced in calibre by fibrous stenosis and the lower lobe bronchi showed moderate dilatation.

The examination of the cranial cavity showed no gross or microscopical evidence of meningitis. In the right temporal lobe there was a chronic abscess cavity about 8 x 6 x 4 cm. in dimensions, containing thick yellow pus of homogeneous consistency. The abscess apparently did not communicate with the ventricle at any point. It had involved a portion of the insula and the outer edge of the lenticular nucleus. Otherwise it appeared limited to the subcortical white matter, except at the anterior tip of the temporal lobe, where the cortex was penetrated in some degree.

Microscopical study of sections from the cerebral abscess showed in the main a heavy wall, chiefly of connective tissue and some intermingled astrocytes. Oedema and some softening were present. The rate of progress of the abscess, as indicated by the degree of perivascular infiltration in different portions of the wall, varied from very slight to considerable. At the tip of the temporal lobe there was much surrounding pressure atrophy of white and gray matter, and adjacent cortex showed marked degenerative changes of nerve cells. The abscess cavity contained acute cellular exudate of polymorphonuclear type. There was no evidence of tuberculous aetiology. The comment of the pathologist was that the abscess appeared "considerably older than the history of cerebral involvement."

Smears of pus from the brain abscess revealed large numbers of intracellular gram positive cocci, which proved upon culture to be staphylococci. Though direct smears were negative, guinea pig inoculation gave a positive result for tubercle bacilli.

Microscopical evidence of miliary tuberculosis was found in the liver and spleen.

The pathological diagnosis was as follows: (*1*) Chronic abscess of the right temporal lobe. (*2*) Pulmonary tuberculosis with extensive fibro-atelectasis on the left, bilateral cavitation and bilateral tuberculous bronchiectasis. (*3*) Miliary tuberculosis of liver and spleen.

DISCUSSION

A multitude of cases have been reported in which metastatic brain abscess occurred complicating various suppurative conditions of the lung and pleura, notably bronchiectasis. However, a careful search of the literature yields only 21 instances in which metastatic brain abscess was thought to have occurred in the presence of pulmonary tuberculosis. Three of the 21 brain abscesses were definitely tuberculous. Of these the case of Fränkel (1) is of interest, in that the abscess showed no gross or histological evidence of tuberculosis, but the pus contained innumerable tubercle bacilli and no other organisms. Fränkel considered this as an example of softening in a tuberculoma. Of the cases in which tuberculosis is not given as the aetiological factor, 9 were published before 1882, the date of Koch's publication of the discovery of the tubercle bacillus. In all of these the aetiology is uncertain. Of the remaining 9 cases, published since 1882, in only 2 is a causative organism mentioned. One of these is the case described by Horst (2) in which pulmonary tuberculosis was complicated by suppuration of a bronchial lymph node, and streptothrix were found in both the brain abscess and the lymph node. The second is described by Rousseau and Giroux (3) and is a case of pulmonary tuberculous cavitation with ulcerative endocarditis and staphylococcic abscesses in the brain and other organs. In none of these cases were complete bacteriological studies made, including culture or animal inoculation for tuberculosis.

Several authors have commented upon the comparative rarity of abscess of the brain secondary to pulmonary tuberculosis. Gowers in 1888 said, "It [cerebral abscess] never results from true tuberculous cavities." Schorstein ventures the suggestion that the tendency of the tuberculous process to obliterate vessels might account for the rarity of metastases. Since bronchiectasis is the most common precursor of metastatic brain abscess, it is of interest that in 3 of the 21 cases cited above, tuberculous bronchiectasis is mentioned, and in 2 the pulmonary cavitation was basal and may have been in part bronchiectatic.

The present case is apparently one of metastatic abscess of the brain, and the only apparent source of the cerebral infection is the tuberculous disease in the lung. A certain amount of tuberculous bronchiectasis was present, particularly in the atelectatic left lung. Also, haemoptysis had been a prominent feature in this case, indicating incomplete vascular occlusion in the region of the lung cavities. Bronchiectasis and haemoptysis, however, commonly accompany tuberculosis in the lung and are hardly sufficient to explain why this patient developed the rare complication of brain abscess. The pathologist who examined

the brain expressed the opinion that the "most suggestive possibility for the source of this pyogenic process would seem to be some infection of the pleura or thoracic wall during some of the surgical procedures." There was, however, no evidence of such infection in this case.

The brain abscess in this case was predominantly staphylococcic, these bacteria being numerous in the pus, while the histological appearance of the abscess wall gave no suggestion of tuberculosis. The finding of tubercle bacilli by guinea pig inoculation, although possibly due to contamination of the specimen, is in keeping with the finding of miliary tuberculosis in other organs of this patient. It is possible, though unlikely, that the abscess resulted from a tuberculoma of the brain secondarily infected by staphylococci.

I am indebted to Dr. J. C. McCarter of the Department of Pathology, University of Wisconsin, Madison, for descriptions of the gross and microscopical appearance of the cerebral abscess in this case.

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STATISTICAL DATA

Edited by MARY DEMPSEY

TUBERCULOSIS DEATH RATE DECLINES SLIGHTLY IN 1942

The Statistical Bulletin of the Metropolitan Life Insurance Company for January, 1943 has published for the country as a whole the first provisional death rate from tuberculosis for 1942. Among the more than sixteen million industrial policyholders of the Metropolitan, 41.7 per 100,000 died in 1942 of tuberculosis, all forms, compared with 42.8 in 1941. When tuberculosis of the respiratory system alone is considered, the death rate declined from 38.9 in 1941 to 37.6 in 1942.

These decreases are slight but one must realize that the industrial policyholders are to a large extent concentrated in industrial centres where an actual increase in tuberculosis was feared. In view of this circumstance, it is probable that the decline in the death rate from this disease will prove to be general throughout the United States when final figures, which include rural residents, are published by the Bureau of the Census.

Among the industrial policyholders of the Metropolitan, tuberculosis was the sixth cause of death in 1942, and pneumonia, with a death rate of 29.4, was seventh. On the other hand, final census figures for 1942 will undoubtedly reverse the position of these two causes of death.

It seems highly probable that the numerous residents of rural regions are not being given sulfa-drugs as a treatment for pneumonia to the same extent as are the industrial policyholders. Not only are these policyholders urban residents as a rule, but they are provided with a visiting-nursing service. These facts indicate that the new type of treatment for pneumonia is presumably much more general among the group reported upon by the Metropolitan Life Insurance Company.

The Statistical Bulletin sounds a warning note when it states: "A rise in mortality (from all causes) is apparently inevitable as the war continues."

ANALYSIS OF 300 MEN IN BRITISH ARMED FORCES WHO WERE FOUND TO HAVE TUBERCULOSIS

A recent analysis[1] of 300 consecutive British service men who were admitted to sanatoria for treatment of pulmonary tuberculosis has resulted in renewed emphasis on the need for X-ray examination prior to enlistment in the armed forces. More than 70 per cent of these cases proved to be actively tuberculous within a year of the time when they were considered fit for the service and an even larger proportion were moderately or far advanced at the time of diagnosis.

[1] J. H. Crawford: Pulmonary Tuberculosis in Servicemen: Analysis of 300 Cases, Lancet, July 25, 1942.

In the opinion of J. H. Crawford, M.D., of Leeds, England, two-thirds of the cases ultimately diagnosed as tuberculous could have been discovered at the time of their initial examination if radiological investigation had been part of the routine procedure. Doctor Crawford further states:

"Though no attempt has been made to go into the financial implications of the problem as revealed by this analysis, it is clear that the admission of such men to the services is wasteful and uneconomic, and the cost to the country is out of all proportion to the value of these men as members of the fighting services. They have to be equipped and trained and cost the country a considerable sum of money for short and unsatisfactory periods of service. They constitute a danger to other troops who are necessarily thrown in close proximity to them under camp or barrack conditions. Valuable hospital time and accommodation are taken up by these men before the diagnosis is established and their discharge arranged. Further, there is the financial burden to the state represented by the cost of pensions for a number and the treatment for all."

CURRENT MORTALITY ANALYSIS

The U. S. Bureau of the Census has recently adopted a new plan to publish a wartime index of health conditions throughout the United States based on 10 per cent of the death certificates filed in state divisions of vital statistics. This publication will appear each month approximately seven weeks after the end of the month in which the deaths occurred. For example, the first number which covers mortality data for a four-month period, August to November, 1942, was issued February 8, 1943.

The selected death certificates are analyzed in an effort to detect any departures from previous trends which may indicate significant changes in health conditions. In wartime it is desirable to keep a continuous watch on the course of mortality from a number of different diseases in various parts of the country.

Although slower than some other diseases to react to changes in health environment, the tuberculosis death rate is one that needs to be under continuous surveillance in wartime. During the four-month period covered, however, this death rate was never significantly in excess of the expected rate.

STATEMENT OF THE EMERGENCY BASE HOSPITAL PROGRAM OF THE OFFICE OF CIVILIAN DEFENSE

Prepared at the request of the Committee on Sanatorium Standards of the American Trudeau Society

Wartime experiences in other countries have stressed the necessity for a mutual understanding and a close working relationship between tuberculosis sanatoria and the emergency medical services of the civilian defense authorities. In view of the possibility of enemy action, particularly in the coastal areas, the Medical Division of the Office of Civilian Defense in coöperation with the U. S. Public Health Service is establishing a chain of Emergency Base Hospitals in "safe areas" for the reception of civilian casualties or other patients whom it may be necessary to evacuate from hospitals in cities under enemy attack. There will be no construction of new hospitals but it is planned to adapt, for use as Emergency Base Hospitals, appropriate existing institutions which now provide medical care.

The development of this program will be facilitated by the coöperation of tuberculosis sanatoria with the State Chiefs of Emergency Medical Service and the Regional Medical Officers. Tuberculosis sanatoria agreeing to serve in this program will be asked to make specific plans for expanding their bed capacities in the event of an emergency which requires their activation as Emergency Base Hospitals. It is suggested that expansion may be accomplished by the more economical use of space ordinarily occupied by patients, by converting to patient care certain areas, such as solaria, day rooms and treatment rooms, not ordinarily used for patients, and by transferring certain patients to their homes or other suitable facilities. Periodically, coöperating sanatoria should determine which patients could be discharged or transferred elsewhere in an emergency, with safety to themselves and to the community.

The Medical Division of the Office of Civilian Defense is aware of the fact that tuberculosis sanatoria in Great Britain were used as Emergency Medical Service hospitals and that open cases of tuberculosis were permitted to return to their homes. Some epidemiologists believe that the reported increase in tuberculosis in Great Britain can be accounted for in part by this procedure. The Medical Division of the Office of Civilian Defense intends to avoid any utilization of tuberculosis sanatoria which might subject the civilian population in this country to any such hazard. It is believed, however, that with proper safeguards tuberculosis sanatoria can be used as Emergency Base Hospitals. Special precautions will, of course, be necessary in arranging facilities for the reception of open cases of tuberculosis temporarily removed from sanatoria.

The State Chiefs of Emergency Medical Service and their Hospital Officers are responsible for designating Emergency Base Hospitals, preparing plans and activating the Hospitals in the event of need. In selecting certain hospitals and other medical institutions in the interior of all coastal states for designation

as Emergency Base Hospitals, emphasis is placed upon the relative safety of the area and the accessibility to the urban Casualty Receiving Hospitals from which civilian casualties and other hospital patients could be promptly transferred. The lines of evacuation of hospital populations from the cities to Emergency Base Hospitals is to be determined in collaboration with the military authorities and the state evacuation authorities. The management and control of institutions activated as Emergency Base Hospitals will remain the responsibility of their governing boards or agencies.

In accordance with the agreement of March 2, 1942, between the Administrator of the Federal Security Agency and the Director of the Office of Civilian Defense, Emergency Base Hospitals will receive payment from the U. S. Public Health Service at the *per diem* rate of $3.75 for all Emergency Medical Service patients. (This is the rate of reimbursement established by the Federal Board of Hospitalization for federal beneficiaries in government hospitals and may be changed if conditions require.) In addition, the Office of Civilian Defense will lend necessary additional beds and matresses from a reserve stock now being stored in warehouses in the coastal states.

The medical staffs of the Emergency Base Hospitals will be supplemented as required by the assignment of affiliated medical units whose members hold inactive commissions in the Reserve Corps of the USPHS. If necessary, a limited number of nurse executives will also be assigned by the USPHS. The members of the affiliated units are being recruited from the staffs of selected civilian hospitals and medical schools. The physicians will be called to active duty only if hospitals in their regions must be evacuated or a portion of the civilian population must be moved because of military necessity.

Detailed problems concerned with the designation and activation of Emergency Base Hospitals, such as routes and methods of transportation of patients, provision of necessary supplementary nonprofessional personnel, and provision of additional equipment, are being studied by Hospital Officers in the coastal states under the direction of their State Chiefs of Emergency Medical Service. Inquiries concerning participation in the Emergency Base Hospital program should be directed to the State Chief of Emergency Medical Service in your state.

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U. S. Office of Civilian Defense
Washington, D. C.
February 18, 1943

NOTICE

War Conference

The medical, surgical and industrial hygiene experts who are so ably safeguarding the well-being of more than 20 million industrial workers have agreed to pool their knowledge and exchange their experiences regarding the many new and complex problems of today's wartime production. For this purpose their organizations

The American Association of Industrial Physicians and Surgeons,

The American Industrial Hygiene Association, and

The National Conference of Governmental Hygienists

are combining their annual meetings in a four-day WAR CONFERENCE at Rochester, New York, May 24–27, 1943. Among the problems to be discussed from a practical standpoint are:

The mass entry of women into industry;

Older-age employees, with their various associated problems; proper placement and employability considerations of the 4F rejectees;

Rehabilitation and proper employment of those already discharged from the military services because of disabling conditions;

Toxic and other hazards from new substances, new processes, and the use of substitute materials;

Absenteeism; fatigue; nutrition;

Effects of long hours; double shifts; two-job workers; overtime; increased industrial accident rates;

Advances in the treatment of illnesses and injuries, and many others.

This joint meeting will be a report on the state of the nation, by the men who know, in matters of industrial health. Dr. William A. Sawyer, Medical Director of Eastman Kodak, is General Chairman; Dr. James H. Sterner and Lieut. Com. J. J. Bloomfield are arranging the programs for the industrial hygienists.

Physicians and surgeons, hygienists, engineers, nurses, executives—all who are interested in the problems of industrial health and their solution—are invited to attend as many of the sessions as they can arrange for; no registration fee is required.

TWIN STUDIES ON THE SIGNIFICANCE OF GENETIC FACTORS IN TUBERCULOSIS[1, 2]

FRANZ J. KALLMANN AND DAVID REISNER

I. GENERAL GENETIC ASPECTS OF THE STUDY[3]

In the study of genetic mechanisms which may play a rôle in the development of tuberculosis, one must bear in mind that the effects of hereditary and nonhereditary factors in the origin of human morbid conditions cannot be expected to operate in a mutually exclusive fashion or to interact in a simple manner.

Regardless of the type of inheritance involved, modern genetic research has discarded the belief that the production of a trait by hereditary elements (genes) precludes variations in the manifestations of the trait as a result of specific environmental influences. Likewise there is no reason to infer from the knowledge of one or more causative agents of a nongenetic nature that heredity does not play a definite part in the causation of the disease in question. It is in line with the biological laws of adaptation that, in relatively common inherited disorders, the coacting rôles of heredity and environment may be as essential as "fuel and oxygen are necessary for making a fire" (Woodworth (31)).

The possible significance of hereditary agents in the aetiology of tuberculosis, therefore, should not be minimized only because exposure to infection is known to be one important factor in the production of the disease. The practical result of such a tendency might simply be a depreciation of pathogenetic knowledge rather than a reëmphasis of the basic rôle played by the tubercle bacillus in the accepted scheme of causation. On the other hand, any success in the identification of genetic factors which may modify the individual vulnerability to the infectious agent would be of very little value without a real understanding of those specific biological conditions which classify tuberculosis as an infection and imply that the acquisition of a certain number of bacilli is a prerequisite of the disease.

The problems caused by this intricate interaction between infectious agents and the genetically determined resistance factors of the individual are further complicated by various uncertainties concerning the type and specificity of the hereditary mechanism or mechanisms which may be involved in the development of tuberculosis. Genetically, a fundamental distinction is made between that specific form of susceptibility determined by a single morbid gene having a large effect, and the varying minus variants of a multifactorial genetic mechanism which result in different degrees of susceptibility to a disease by reason of deficiencies in normal resistance. When many genes interact to produce a graded character such as resistance to infection, their individual effects will be neither

[1] From the New York State Psychiatric Institute and Hospital and from the Bureau of Tuberculosis, New York City Department of Health, New York, New York.

[2] Presented in part before the Medical Section at the 38th annual meeting of the National Tuberculosis Association, Philadelphia, May 8, 1942.

[3] The study was supported by grants from the Carnegie Corporation of New York and the National Tuberculosis Association.

potent nor pathogenic, and their interaction will usually be in the direction of a normal state, which in tuberculosis will be a satisfactory state of protection against tubercle bacilli. A pathological state will be produced by these genes only if there is an imbalance either in their original arrangement or in the efficiency of their protective interaction.

A single morbid gene may be dominant or recessive in the manner of its inheritance and it may be completely or incompletely penetrant in its appearance in the life of the individual; but the main implication of such a single factor for a specific susceptibility is that an individual cannot develop the disease without being a carrier of the particular gene. Since it is commonly held, however, that no human being is absolutely immune to tuberculosis, it would follow in the case of single-factorial inheritance, as assumed by Diehl and Von Verschuer (8), that there must be two distinct forms of tuberculous disease; namely, an inherited form developed under ordinary conditions of exposure by persons carrying the specific gene, and a nonhereditary form produced in any individual by an overwhelming infection.

The assumption of two different forms of tuberculosis would not be necessary, if variable resistance to the disease were the result of multifactorial inheritance. The existence of a heredoconstitutional defense mechanism resulting from the interaction of many genes would suffice to explain why the effect of heredity in tuberculosis seems to be of a graded character, ranging from the greatest to the least possible degree of resistance. Since the inherited capacity for the development of high resistance cannot be thought of as providing more than a relative degree of immunity, it is not difficult to see, in terms of multifactorial inheritance, that the protective system of even a highly resistant person will break down if subjected to massive infection or repeated inoculations.

There is still another complicating feature which is to be considered in the genetic analysis of tuberculosis. Theoretically it is possible that hereditary effects may be associated with the operation of different genetic principles at various stages of the tuberculous process. It may be necessary, for instance, to make a distinction between varying degrees of resistance to the invasion of the tubercle bacillus and varying degrees of resistance to the spread of the established disease. If it could be shown that there actually exists a genetically determined inability to resist tuberculous infection as well as an innate inability to resist the progressive disease, then two such genetic mechanisms—distinguished as *Anfälligkeit* and *Hinfälligkeit* in the German terminology—cannot be assumed to be identical without conclusive biological evidence of their identity.

The need for a thorough clarification of this possible interplay of genetic and nongenetic factors in the determination of variable resistance to tuberculosis is emphasized by a number of clinical and experimental observations. The clinical evidence in support of heredity includes the generally accepted fact that variations in epidemiological and other environmental conditions alone are unable to explain the consistent differences in tuberculosis morbidity and mortality among certain racial groups.

There is also the common experience that exposure to infection, although basically important in the causation of the disease, often does not suffice to produce

manifest tuberculosis. Especially significant in this respect is the failure of many marriage partners of tuberculous patients to develop clinical disease despite most intimate and prolonged exposure. On the other hand, manifest tuberculosis is frequently found in the absence of any known contact history, even if careful inquiries are made to determine the actual source of infection. Evidently, however, although these and other observations indicate variability in individual susceptibility or resistance to tuberculosis, no one of them is by itself sufficiently conclusive to substantiate a clearly genetic theory.

More pertinent in this respect are data obtained by experimental methods, especially the findings observed in animal experiments and twin studies. There may be certain objections to a direct comparison between the pathogenetic conditions of spontaneous human infections and those artificial infections produced in inbred animal stocks. To some extent one may also be justified in questioning the statistical accuracy and genetic interpretation of certain earlier twin investigations. It may even be debatable if it is quite correct to classify the unqualified twin study method as "experimental," since it is a natural phenomenon rather than human ingenuity which provides in twins an opportunity to analyze the relative effects of heredity and environment. Unquestionably, however, the results obtained by the different methods of approach in twin studies and animal experimentation correspond closely in demonstrating the significance of heredoconstitutional factors in the determination of variable resistance to tuberculosis. It cannot be denied, therefore, that the execution of careful control investigations is definitely indicated and, at the present state of limited genetic knowledge, rather urgently needed.

Among the animal experiments which have been indicative of genetically determined variations in resistance to tuberculous disease, Lurie's work (14, 15, 16) in inbred rabbit stocks, continuing the pioneer studies of Lewis and his associates at the Phipps Institute, deserves particular attention. Consistent inbreeding of ordinary rabbits led to the development of three distinct family groups: namely, a highly resistant family displaying a localized, chronic, ulcerative form of pulmonary tuberculosis, analogous to the human reinfection type; several nonresistant families with rapidly progressive, primary, generalized disease; and some moderately resistant families showing various intermediate forms of the disease. Lurie concluded, therefore, that the "resistance of rabbits to naturally or artificially acquired tuberculosis is largely controlled by their genetic constitution, although it may be overwhelmed by large doses of tubercle bacilli." The main variant in the type of disease developed by the three different family groups was seen in the extent of localization of the infection at the portal of entry.

These consistent variations in the inherited resistance of rabbits were found by Lurie to be closely related to the intensity and rapidity by which local immunity was acquired by the tissues of the respective families. Other varying factors revealed as being associated with the two extreme degrees of resistance were high or low skin permeability, rapid or slow development of allergic sensitivity and intense or tardy production of antibodies.

It is the mononuclear cells which in highly resistant rabbits are assumed by

Lurie to possess the capacity for inhibiting the growth of the bacilli to such an extent as to prohibit their multiplication in organs focalized by lymphogenous or haematogenous routes. There is a fulminating progression of the primary focus in nonresistant families, as their mononuclears are unable to interfere with the growth of the bacilli in their cytoplasm. No one of the rabbit families of intermediate resistance is said to have shown such extreme variations in the ability or inability of their mononuclear cells to develop inhibitory properties against the multiplication of bacilli in their cytoplasm.

Whether or not Lurie is correct in suggesting that "the sum total of numerous determinants controls hereditary resistance to tuberculosis in rabbits," and that "the disease types observed in rabbit families of varying inherited resistance are essentially analogous to the different types of tuberculosis developed by different human ethnic groups," the general genetic significance of his findings in rabbits would be unquestionable if similar inherited variations in resistance to tuberculosis could be shown to exist in spontaneous human infection. In order to carry out these essential studies, the only "experimental" method directly applicable in man is the twin method. The comparison of unselected groups of one-egg and two-egg twin pairs provides a truly controlled situation which is indispensable for an objective analysis of the variable effects of genetic potentialities in human tuberculosis.

The emphasis of the twin method rests upon the distinct hereditary differences between the categories of monozygotic (identical) and dizygotic (fraternal) twins. Monozygotic twins are derived from a single fertilized ovum which splits into two halves at a very early stage of embryonic development, each half carrying precisely the same complement of genes. They are always of the same sex and are genetically as identical as the right and left halves of one individual. Frequently they resemble each other so closely that it is practically impossible to tell them apart.

Dizygotic twins arise from two separate ova, which have happened to mature and to be fertilized simultaneously. They are genetically like any other pair of brothers and sisters who are born at different times (siblings), and may be of the same or of opposite sex. Their genotypes cannot be expected to be composed of the same genes more frequently than those of ordinary brothers and sisters.

Under usual conditions, both types of twins are likely to share about the same environment. Consequently, if an intra-pair difference is greater for dizygotic than for monozygotic twins, the fundamental cause for this difference must be sought in heredity, although it is to be expected, as Woodworth (31) has put it, "that environmental factors may accrue to heredity as interest accrues to legacies of different amounts."

The usefulness of the twin method naturally depends upon the possibility of distinguishing reliably between the two categories of twin pairs. The only method used at present for classifying twin partners in respect to their zygotic origin is the modern similarity method, since it is known now that not all of the monozygotic twin pairs are necessarily monochorial. If twinning occurs at a very early stage of development, two separate chorions may be developed even by monozygotic twins, although it is the rule only for dizygotic twins.

It is obvious, of course, that this recent discovery has merely discredited the old fetal-membrane method and does not reflect upon the basic genetic principle that the two types of twins exist. The indisputable evidence of their existence includes the occurrence of conjoined Siamese twins, the distribution of sex ratios in unselected groups of twin pairs and the fact that certain twin partners are so identical that it is inconceivable that they could arise from two distinct eggs with different assortments of genes from their parents.

Conclusive proof of monozygocity is obtained by comparing the twin partners in a series of variations in clearly distinguishable anatomical traits, which are determined by heredity without being too common in the population. If the chances of two siblings or fraternal twin partners being alike in a variation of one such trait is 1 in 2, the chances of their being alike in ten such traits is 1 in over 1,000 (Woodworth). Among the traits used are hair and eye color, hair form and hair texture, blood group, facial features, arrangement of teeth, skin color and skin texture, proportions of hands and fingers, and the microscopical characteristics of finger and palm patterns. There must be stronger cross-resemblance than internal resemblance in most of the details of fingerprints; that is, one hand of one twin must be more like one hand of the other twin than like his own other hand. According to Newman (17), the presence of reversed asymmetry in handedness, dentition and palm patterns is confirmatory evidence of monozygocity, but its absence does not exclude it.

It may happen, of course, but very rarely, that two dizygotic twin partners inherit almost the same combination of physical characteristics, especially if their two parents are genetically very much alike. However, the chances of misdiagnosing dizygotic twins as monozygotic are negligible. The mistakes which are more likely to occur in practice are those of diagnosing some of the least similar monozygotic twins as dizygotic. But even this error is not apt to be made by investigators who are sufficiently experienced in twin diagnosis and who do not attempt to classify their twin cases on the basis of any single sign.

The common objection, that a difference in tuberculosis morbidity between one-egg and two-egg cotwins (partners of twin index cases[4]) might be adequately explained by a more intimate contact in monozygotic twin pairs, is valid at best for twin studies which are numerically limited and open to errors from unrepresentative samples. In statistically representative surveys this argument can be met by sampling suitable subgroups, especially by comparing twins of the same and of opposite sex, twins reared together and reared apart, and twins with and without exposure to a common source case. While any intra-pair difference between monozygotic twin partners must be attributed to variations in external or dispositional influences, an intra-pair difference which is greater for opposite-sexed than for same-sexed sets of dizygotic twins may be due either to genetic or nongenetic factors associated with the difference in sex.

[4] The term "index case" is used in this study in preference to, but synonymously with, the more customary genetic term "proband," designating those original cases in a family survey which constitute the starting point of the study and, therefore, must be proved representative of the type of trait-carrier whose relatives are to be investigated as to the recurrence of the trait under observation.

This scope of the original twin method can be broadened still further if the number of genetically dissimilar sibship groups reared under comparable environmental conditions is extended to include full siblings (with two parents in common), half-siblings (with one parent in common), and step-siblings (not related by blood) of the twin index cases. Such a combination of a twin and family survey has been adopted in this study and may be called "Twin Family Method." It provides six distinct categories of sibship pairs: namely, monozygotic twins, dizygotic twins of the same sex, dizygotic twins of opposite sex, full siblings, half-siblings, and step-siblings. If the assumed genetic mechanism exists and the part played by the twinning factor is negligible, the statistical expectation will be that the concordance[5] rates for dizygotic twins should closely correspond to the morbidity rates for full siblings, but should distinctly differ from the rates for the other sibship groups.

Of course, such a detailed analysis requires an extensive and unselected material, while most of the previous twin investigations have been limited either numerically or methodologically. The majority of these studies were case reports of single twin pairs which happened to be concordant or discordant as to certain clinical aspects of the disease, and the few remaining ones were either restricted as to the size of the material or questionable as to the criteria of selection used. Nevertheless, their findings seemed to confirm what had already been suggested by the genealogical investigations of Weinberg (29), Riffel (19), Doyer (10) and others; namely, that the closest blood relatives of tuberculous patients tend to develop clinical tuberculosis more frequently, and even not uncommonly in a more similar form, than is observed in members of the general population under comparable conditions of exposure.

Of the individual twin cases so far reported in the literature, the pairs of Bauer (4), Kretschmer (13), Czarnecki (7), Kettelkamp and Stanbro (11), Klein (12), Siemens (23), d'Almeida (2), Schaefer (22) and Valdés-Lambea (27) seem to have been monozygotic and concordant; those of Alons (3), Roessle (21), Czarnecki (7) and Stamm (25) were probably dizygotic and concordant; and that of Curtius and Korkhaus (6) was later diagnosed by Diehl and Von Verschuer (9) as dizygotic and discordant. The cases described by Ahlfeld (1), Rivers (20) and Orgler (18) were so incomplete as to the data on zygocity that they cannot be classified at all. The reports of Schokking (24) on 9 pairs and of Bossik (5) on 117 pairs were confined to observations in children. The main conclusion of Bossik's survey, which was conducted at the Maxim Gorky Medico-Biological Research Institute in Moscow, was that hereditary factors play a part in susceptibility to infection and in the reaction of the host to the microörganism, since the monozygotic twins showed simultaneous occurrence and similarity in the course of primary tuberculosis more frequently than did the dizygotic twins.

Of the two remaining twin studies dealing with clinical tuberculosis in adults, that of Uehlinger and Kuensch (26) was based on 46 pairs, of which 12 were classified as monozygotic and 34 as dizygotic. Concordance as to tuberculosis

[5] Similar behavior of two twin partners in regard to the trait under observation.

was observed in 58.3 per cent (7 pairs) of the one-egg sets and in 5.9 per cent (2 pairs) of the two-egg sets. Discordance as to tuberculosis was found in 5 monozygotic and 32 dizygotic pairs, while similarity in environment was reported in 7 of the 12 monozygotic pairs and in 25 of the 34 dizygotic pairs.

More conclusive were the results obtained by Diehl and Von Verschuer (8, 9) in a survey, which may be rated as statistically representative, although it included only the twin partners of the index cases and was not quite consistent in the selection of cases. Their twin material originally consisted of 127 pairs, but later was enlarged to 205 pairs. Of this total number, however, only 134 sets in the final material and 77 sets in the original material were unselected cases of active ("progressive") clinical tuberculosis ("exclusive of healed primary infections"). In a separate analysis of these various groups the difference in concordance as to tuberculosis between one-egg and two-egg twin pairs ranged from 25 to 70 per cent for the first series of 77 unselected pairs, from 21 to 60 per cent for the total group of 134 unselected pairs, and from 25 to 65 per cent for all 205 pairs studied. These consistent and statistically significant variations in the concordance rates of the two categories of twin partners were shown to be due to the genetic rather than environmental differences between monozygotic twin pairs. The authors concluded, therefore, that hereditary factors play a decisive rôle in both the origin and the clinical course of tuberculous disease.

The genetic mechanism involved was assumed by Diehl and Von Verschuer to be definitely specific and "most probably not of a multifactorial nature," while its modifying effect on the "natural resistance to tuberculous infection" was found to become more pronounced with increasing age. No final attempt was made to analyze the given type of inheritance or the morphological aspects of the inherited factor for susceptibility to tuberculosis in any particular details.

All of these observations indicate the significance of genetically determined variations in susceptibility or resistance to tuberculous disease. The fact remains, of course, that tuberculosis is an infectious disease caused by a specific microörganism and, therefore, modifiable by any environmental conditions, biological and socio-economic, which may influence infections in a given population. Nevertheless, it is necessary to clarify the important part which seems to be played by genetic factors in the variability of the pathological effect produced by the tubercle bacillus. At present, no better method is available for this purpose than the "Twin Family Method."

II. THE ORGANIZATION OF THE STUDY

In order to obtain statistically representative material for the application of the Twin Family Method, the study was organized on a long-term, state-wide basis. The twin index cases were collected from the resident populations and new admissions of the tuberculosis hospitals as well as from the patients of the tuberculosis clinics in the State and City of New York. The danger of major technical selective factors in the sampling of the material was avoided by referring the determination of the index cases to the staffs of the hospitals and clinics coöperating in the survey. Their collaboration was procured through the

courtesy of the respective departmental executives in the New York State Department of Health and the New York City Departments of Health and Hospitals.

In the procedure of collecting the twin index cases, no attention was paid to the survival, health status or availability for personal examination of the twin partners. This precaution was necessary in order to avoid an excess of cases whose twinning status had become known because of conspicuous features in their concordance as to tuberculosis or any other finding of special clinical interest. Another precautionary measure consisted of excluding from the statistical survey proper those twin cases who had not been reported through official channels. The only criteria for selection of the index cases were, therefore, that they be born by multiple birth and that they had come under observation of one of the coöperating agencies with the diagnosis of tuberculosis. Accordingly, residence of one member of a set of twins in an institution located within the State of New York, rather than legal residence of a twin patient or his family in this state, served as the accepted standard in the limitation of the material.

The diagnostic aspects of the study were strictly a matter of the investigators' research, since it was advisable to ascertain them beyond reasonable doubt and in accordance with a uniform system of classification. Whenever possible, therefore, the diagnosis of both tuberculosis and zygocity was made on the basis of personal examination and extended observation. The clinical data required for a diagnosis of tuberculosis included complete histories, chest X-ray films and sputum examinations. No information essential for clinical or genealogical classifications was ever accepted without substantial evidence secured by personal visits, regardless of whether these data were obtained from hospital records, the patients themselves or any of their relatives. Nor was it consistent with the rules of the investigation to classify any person included in the survey as free from clinical disease without the availability of current normal roentgenograms and a detailed history of exposure. Systematic efforts were also made in every case to collect the birth records and childhood photographs of the twins, although the final twin diagnosis was always based on the personally obtained results of the similarity method rather than on descriptions, impressions or the fetal-membrane method.

The practical efficiency of this system is demonstrated by the total number of 657 twin cases reported within a period of less than five years, and by the distribution of monozygotic and dizygotic sets in the total group of 308 twin pairs used in the statistical part of the report on reinfection tuberculosis (table 1). There are 78 monozygotic and 230 dizygotic twin pairs with manifest reinfection tuberculosis in at least one member or, more precisely, 308 pairs constituted by 616 twins, of whom 334 were index cases affected by reinfection tuberculosis. Of the 230 two-egg sets, 118 are same-sexed and 112 are opposite-sexed.

The random sampling of the total material is indicated by the close correspondence between the statistically expected figure of 25.6 per cent for the proportion of monozygotic twin pairs in an unselected American twin group and the corresponding figure of 27.3 per cent as calculated according to the Weinberg Dif-

ferential Method for the material of the present study. The main principle of this method is that there should be equal numbers of same-sexed and opposite-sexed twin pairs in the absence of one-egg pairs. Therefore, in multiplying the number of boy-girl pairs by two and subtracting this product from the total number of pairs under observation, that is, 308 minus 224 in the present instance, one obtains that comparable figure for the proportion of monozygotic sets which should, and in this material practically does, correspond to the rate expected in a general population group.

It is also in accordance with statistical expectation that different ratios of white to nonwhite cases were observed in the upstate and metropolitan areas which reported totals of 368 and 289 twin cases, respectively. Of the 209 tubercu-

TABLE 1

Regional and racial distribution of the twin index cases

	ALL TWIN CASES REPORTED								COMPLETE TWIN PAIRS WITH REINFECTION TUBERCULOSIS			
			Tuberculous index cases							Dizygotic		
	Total number of cases reported	Contact cases without manifest tuberculosis	Primary tuberculosis	Reinfection tuberculosis		Racial distribution		Total number of tuberculous cases reported	Monozygotic			Total number of pairs included in study of reinfection tuberculosis
				Incomplete*	Complete	White	Nonwhite			Same-sexed	Opposite-sexed	
New York City	289	80	14	49	146	144 (68.9%)	65 (31.1%)	209	35	54	47	136
Upstate New York	368	93	23	64	188	262 (95.3%)	13 (4.7%)	275	43	64	65	172
Total number	657	173	37	113	334†	406 (83.9%)	78 (16.1%)	484	78	118	112	308†

* Twin partners were unavailable at the time of disease onset in the index cases.

† The difference between 334 "index cases" and 308 "index pairs" is due to the fact that in 26 pairs both twin partners were reported as index cases and acceptable as such.

lous index cases from the New York City area, 31.1 per cent were classified as nonwhite, their vast majority being Negroes. The corresponding rate for the 275 twin patients reported by agencies in the upstate area is only 4.7 per cent.

The ratio of white to nonwhite twin cases for the total material is about 5:1 and of significance in this analysis mainly because it was taken as the basis for computing a corrected morbidity figure valid for a general population with comparable age and racial distributions. The need of such a statistical correction is evident in a survey which requires comparison of collective morbidity rather than age-specific mortality rates, although it includes genealogically diverse kinship groups, such as parents and siblings of the index cases.

It is shown in table 2 that the fact of being the parent of a tuberculous index case practically eliminates this person's chance of dying from tuberculosis before

the age of twenty-five, while the siblings of the index cases reach the peak of their tuberculosis mortality between the ages of twenty and twenty-four. Obviously, the morbidity figures for such heterogeneous relationship groups, collected through index cases, affected by tuberculosis or any other trait not manifested at birth, cannot be directly compared either with each other or with a general population rate, unless they are corrected for major differences in age distribution by the same statistical method. In fact, the uniformity of this corrective procedure may be considered more essential than any technicality of its application.

Consistency in the correction of all group differences in age distribution has been obtained in this survey by the use of the Abridged Weinberg Method (30).

TABLE 2

Tuberculosis mortality in the siblings and parents of the index cases

AGE GROUP	SIBLINGS OF INDEX CASES						PARENTS OF INDEX CASES					
	All siblings			All manifest tuberculosis cases		Ratio of tuberculosis deaths to all deaths	All parents			All manifest tuberculosis cases		Ratio of tuberculosis deaths to all deaths
	Total number	Living	Dead	Living	Dead		Total number	Living	Dead	Living	Dead	
						per cent						*per cent*
0- 4	147	—	147	—	—	—	—	—	—	—	—	—
5- 9	21	6	15	—	2	13.3	—	—	—	—	—	—
10-14	42	32	10	2	4	40.0	1	—	1	—	—	—
15-19	104	74	30	6	25	83.3	1	—	1	—	—	—
20-24	130	112	18	16	17	94.4	2	—	2	—	—	—
25-29	138	122	16	13	10	62.5	19	—	19	—	11	57.9
30-34	131	119	12	15	10	83.3	15	—	15	1	4	26.7
35-39	85	79	6	6	2	33.3	34	10	24	6	12	50.0
40-44	44	38	6	6	4	66.7	98	48	50	10	18	36.0
45-54	56	50	6	2	4	66.7	165	88	77	6	21	27.3
55-64	22	16	6	—	—	—	197	139	58	15	4	6.9
Over 64	10	10	—	—	—	—	156	94	62	2	4	6.5
	930	658	272	66	78	28.7	688	379	309	40	74	23.9

This method relates the absolute morbidity figures to the total number of persons who have survived a given period of manifestation, increased by one-half of those persons who at the time of the study were still within the age limits of this period. The resulting morbidity rates are average expectation figures valid for persons above the chief manifestation period, which in reinfection tuberculosis was conservatively assumed throughout this study to extend from the age of fifteen to twenty-nine.

An extension of the manifestation period in reinfection tuberculosis, which occurs mainly before the age of thirty, would naturally enlarge the difference between absolute and corrected morbidity rates, since the given statistical rate of reference includes only one-half of the persons observed in this period and

omits entirely the persons who are below the age of fifteen, regardless of whether they are deceased or living. An overextension might even be expected to affect the statistical accuracy, since the usefulness of the Abridged Weinberg Method depends no less on a relatively uniform distribution of the persons observed within the accepted period of manifestation than it depends on a representative size of the total material studied.

The use of this method in determining an estimated tuberculosis morbidity rate for a general population, which in age and racial distributions is comparable to that of the State of New York, yields a corrected rate of 1.37 per cent, while the absolute figure is 1.08 per cent (table 3). Both figures have been obtained by multiplying by ten for the white and by five for the nonwhite the present age-specific annual death rates as compiled by the U. S. Bureau of the Census. The

TABLE 3

Expected tuberculosis morbidity in the State of New York

AGE GROUP	TUBERCULOSIS DEATH RATES PER 100,000 AS OF JULY 1, 1939 (U. S. BUREAU OF THE CENSUS)				MORTALITY PER 100,000 OF A POPULATION CONSISTING OF FIVE-SIXTHS WHITES AND ONE-SIXTH NONWHITES		ESTIMATED MORBIDITY PER 100,000		TOTAL MORBIDITY EXPECTATION FOR GENERAL POPULATION		
	White male	White female	Non-white male	Non-white female	Five-sixths white	One-sixth non-white	1:10 white	1:5 non-white	Corrected rate of reference	Uncorrected	Corrected
15–19	9.71	11.88	206.57	247.03	18	76	180	380	50,000	—	—
20–24	22.97	35.48	322.48	269.86	48	99	480	493	50,000	—	—
25–29	28.62	32.67	181.96	259.68	51	74	510	367	50,000	—	—
30–34	43.08	25.11	336.59	194.65	57	89	570	443	100,000	—	—
35–44	66.94	21.80	404.48	106.44	74	85	740	425	100,000	—	—
45–54	120.14	26.29	351.35	197.25	122	91	1,220	456	100,000	—	—
55–64	100.33	24.11	293.26	57.65	103	59	1,030	292	100,000	—	—
Total....	52.32	21.85	244.76	160.70	473	573	4,730	2,856	550,000	1.08	1.37

use of a higher multiplier for whites than for nonwhites has been considered necessary because the generally more rapid and destructive course of the disease in the Negro may be expected to result in a lower ratio between annual morbidity and mortality figures in the nonwhite than in the white population.[6]

Of course, this estimated general morbidity rate is only a crude maximum figure for a population consisting of five-sixths whites and one-sixth nonwhites. It does not compare with general morbidity rates obtained by direct sampling

[6] To explain this statistical procedure in more detail, one may say that it attempts to estimate the incidence of morbidity from the incidence of mortality, since direct data are available only for mortality at the present time. It is known that, of two groups of whites and Negroes developing tuberculosis in a given year, the Negroes will show a higher proportion of deaths. Consequently, in estimating the incidence of morbidity one has to multiply the Negro death rate by a figure which is lower than the one used in the white rate. The multiplier accepted in the study is one-half of the figure used in the white rate.

methods, although it may be used in the absence of more accurate morbidity figures for unselected population groups. It may be possible later on to secure a more exact general population rate for this survey by the subsequent inclusion of both the siblings of the marriage partners and the step-siblings of the index cases.

Meanwhile, however, there seem to be no valid reasons against using a general morbidity figure of about 1 per cent for the particular comparative purposes of the present study. The differences in the collective morbidity rates for the various groups of the given material are so pronounced that their statistical significance appears unquestionable and certainly independent of any possible variations in the general morbidity figure used for comparison.

III. STATISTICAL DATA ON REINFECTION TUBERCULOSIS

The material available for analyzing the frequency of tuberculosis among the relatives of twin index cases affected by reinfection tuberculosis consists of 308 complete families (table 4). In addition to 616 twin partners, whose age and sex distributions are shown in table 5, there is an unselected series of 930 full siblings, 74 half-siblings, 688 parents and 226 marriage partners of twin patients, making a total of 2,534 persons who have been investigated with respect to tuberculosis and contact conditions. Another group of 113 twin cases with reinfection tuberculosis cannot be used for statistical analysis, since their twin partners were unavailable at the time of disease onset in the index cases.

The collective morbidity rates for all relationship groups included in the survey are compared in table 6. As regards the uncorrected rates for the siblings and half-siblings it may be noted that they relate to all individuals above the age of fourteen, that is, to 720 siblings and 42 half-siblings who are fifteen years or older. This statistical procedure seems advisable, since the age group from birth to fourteen is not represented in any of the other relationship groups of this survey. When all 930 siblings and 74 half-siblings are used as rates of reference, their collective morbidity figures amount to 13.5 and 5.4 per cent, respectively.

Regardless of whether the uncorrected or corrected rates are taken into account, they clearly indicate that the chance of developing manifest tuberculosis increases in strict proportion to the degree of blood relationship to a tuberculous index case. The respective rates amount to 6.2 and 7.1 per cent in the marriage partners; 9.5 and 11.9 per cent in the half-siblings; 16.6 and 16.9 per cent in the parents; 18.9 and 25.5 per cent in the full siblings; 18.3 and 25.6 per cent in the dizygotic cotwins. The highest morbidity figures (61.5 and 87.3 per cent, respectively) are found in the monozygotic twin partners, that is, in the category of consanguinity implying homozygosis[7] for the given genotype. Their corrected concordance rate expresses the chance for a person above the age of twenty-nine, who is genetically identical with a tuberculous index case and has been exposed to infection, to develop manifest tuberculosis.

[7] A person is homozygous with respect to a genetic factor if the particular gene is inherited from both parents so that the two corresponding gene members of the given pair are alike in this person.

TABLE 4

Classification of persons included in reinfection tuberculosis survey

	TWINS	SIBLINGS	HALF-SIBLINGS	PARENTS	HUSBANDS AND WIVES	TOTAL NUMBER
New York City	272	427	49	292	103	1,143
Upstate New York	344	503	25	396	123	1,391
Total number	616	930	74	688	226	2,534

TABLE 5

AGE GROUP	TWIN INDEX CASES					TWIN PARTNERS				
	Living		Dead		Total number	Living		Dead		Total number
	Male	Female	Male	Female		Male	Female	Male	Female	
15–19	10	6	2	4	22	5	10	—	2	17
20–24	26	44	13	9	92	30	44	5	2	81
25–29	18	36	10	20	84	18	34	1	5	58
30–34	21	21	3	6	51	18	22	—	1	41
35–39	12	10	6	7	35	11	17	1	1	30
40–44	9	8	2	3	22	8	13	1	1	23
45–49	2	4	3	3	12	8	4	—	2	14
50–54	2	2	2	3	9	5	4	—	—	9
55–59	—	1	3	—	4	3	1	—	1	5
60–64	—	1	2	—	3	3	—	1	—	4
Total number	100	133	46	55	334	109	149	9	15	282

TABLE 6

Tuberculosis morbidity rates in the twin index families

	GENERAL POPULATION* OVER FOURTEEN YEARS OF AGE	RELATION TO TUBERCULOUS INDEX CASES					
		Husbands and wives	Parents	Half-siblings	Full siblings	Dizygotic cotwins	Monozygotic cotwins
Number of cases							
Cases of tuberculosis	—	14	114	4	136	42	48
Rates of reference							
Uncorrected	—	226	688	42†	720†	230	78
Corrected	—	197.5	676	33.5	534	164	55
Morbidity rates							
Uncorrected for differences in age	1.08	6.2	16.6	9.5	18.9	18.3	61.5
Corrected (Weinberg method)	1.37	7.1	16.9	11.9	25.5	25.6	87.3

* Estimated for a population in which the ratio of white to nonwhite persons approximates 5:1.

† All individuals above the age of fourteen.

The correlation between consanguinity and frequency of tuberculosis is so consistent that it does not seem possible to explain all these group differences in morbidity merely by a more intimate contact between closer relatives. The sibling figure is about eighteen times higher than the expected general average frequency and also exceeds, possibly in part for reasons of selection with respect to the parents, the respective rates for the half-siblings, parents and marriage partners. The concordance rate for the dizygotic twins corresponds closely with the morbidity rate for the full siblings and shows a distinct difference only from the rates for the other sibship groups. The morbidity figure for the husbands and wives of the twin patients is about midway between the rates for the general population and the half-siblings, although their contact with the index cases may be assumed to be far more intimate than that of the half-siblings. In fact, exposure alone may not account for the total difference between general average

TABLE 7

Average age, exposure and family taint of the index cases

TYPE OF TWINS	AGE AT DISEASE ONSET		EXPOSURE OF INDEX CASES (PER CENT)			FAMILY HISTORY OF TUBERCULOSIS OF NONEXPOSED INDEX CASES (PER CENT)		
	Number of index cases	Average age	Definitely exposed index cases	Index cases with questionable exposure	Non-exposed index cases	Index cases with tuberculosis in direct ancestry	Tuberculosis in collateral lines only	No history of tuberculosis in ancestry
		years						
Monozygotic.....	78	21.3	35.9	11.5	52.6	36.6	22.0	41.5
Dizygotic.....	230	21.8	32.6	12.2	55.2	13.4	26.8	59.8
Total number....	308	21.5	33.4	12.0	54.5	19.0	25.6	55.4

expectation and the morbidity rate for the marriage partners, since marriage to a tuberculous patient statistically represents a definite selective factor with reference to the probability of being affected by the same disease.

In order to exclude the possibility that the marked difference in morbidity between monozygotic and dizygotic cotwins might be sufficiently explained by factors other than genetic, a more detailed analysis of the index cases was undertaken. It is shown in table 7 that the two groups of index cases do not differ significantly in the average age at disease onset, the frequency of exposure, or the ancestral taint conditions with respect to the known incidence of tuberculosis in the preceding generations (family history of tuberculosis).

No history of exposure to another source case has been ascertained in either group for about one-half of the index cases (52.6 to 55.2 per cent). However, in 44.6 per cent of all nonexposed twin patients it is known that there have been additional cases of tuberculosis in the direct or collateral lines of ancestry without personal contact between the twins and their affected blood relatives. This observation is definitely in favor of a genetic theory, particularly since it cannot

be taken as absolutely certain that the family history in the other half of these index cases was really free of tuberculosis.

Concerning the frequency of tuberculosis in the twin partners of the index cases it is revealed in tables 8 to 10 that the collective morbidity rates for the cotwins are modified by a variety of secondary factors, genetic as well as non-genetic, but certainly not to an extent which would explain the marked difference between the two types of twins. In fact, regardless of whether these modifications are associated with race, sex, age or parental taint, they are of similar extent in the groups of the siblings and dizygotic cotwins, but play only a minor rôle in the monozygotic group, thereby emphasizing the genetic nature of the factors for deficient resistance in this category.

It is shown in table 8 that the morbidity expectation among the siblings and dizygotic twin partners is about twice as high for the descendants of tuberculous parents as for the descendants of nontuberculous parents, while this difference practically disappears in the one-egg twin partners. Their morbidity rates are

TABLE 8

Variations in sibship morbidity according to sex and parental taint

	CORRECTED MORBIDITY RATES IN RELATION TO PARENTAL TAINT			CORRECTED MORBIDITY RATES IN RELATION TO SEX					
				Same-sexed sibships			Opposite-sexed sibships		
	Sibships with nontuberculous parents	Sibships with tuberculous parents	Total morbidity rate	Male	Female	All same-sexed persons	Male	Female	All opposite-sexed persons
Siblings.....	18.1	35.3	25.5	24.7	29.5	27.7	19.7	24.4	21.7
Dizygotic cotwins....	18.8	38.6	25.6	27.6	31.6	30.2	18.6	22.7	20.5
Monozygotic cotwins.	85.7	88.9	87.3	76.9	93.3	87.3	—	—	—

unaffected by the possibility of being homozygous for deficient resistance because of having or not having a tuberculous parent. Instead, their chance of developing the disease appears largely determined by the genetic constitution of monozygotic twin partners of tuberculous index cases.

With respect to the marked differences in morbidity as found between the sibships with and without tuberculous parents in the groups of the siblings and dizygotic twins, two possible explanations may be considered to account for the increased morbidity in the sibship groups with tuberculous parent. The increase may be the result of either intensified exposure or the greater statistical chance of inheriting a deficient genotype from a homozygous parent. However, since the factor of additional exposure does not show a significant effect upon the concordance rate of the monozygotic twin partners, it does not seem sufficient to explain the variations in morbidity in the other sibship groups. In fact, if intensified exposure were the main cause of these differences, it would be difficult to understand why the dizygotic twin partners who have had a tuberculous parent in addition to a tuberculous cotwin do not show a higher morbidity rate than the monozygotic twin partners without a tuberculous parent.

Variation in concordance between opposite-sexed and same-sexed pairs cannot exist in the monozygotic twins and is present only to a limited extent in the siblings and dizygotic twins. The range of the former group is from 21.7 to 27.7 per cent, and that of the latter group from 20.5 to 30.2 per cent (table 8). These discrepancies are an indication that fraternal twins belonging to the same sex have a greater chance of being alike in those specific and nonspecific conditions which favor the development of tuberculosis. It is evident, however, that the given sex variations are by no means extensive enough to permit a nongenetic explanation for the entire difference, or a major part of the difference, between the concordance rates of one-egg and two-egg twin pairs.

The excess of female over male morbidity rates in each of the sibship groups is definitely in accordance with statistical expectation. Most of the twin patients and their siblings were between the ages of fifteen and twenty-nine when

TABLE 9

Age variations and time of observation in the twins and siblings

	ALL TUBERCULOUS PERSONS	AVERAGE AGE AT DISEASE ONSET (YEARS)			NONTUBERCULOUS COTWINS AT THE TIME OF EXAMINATION		AVERAGE DURATION OF OBSERVATION (YEARS)	
		Male	Female	Total average age	Total number	Average age	Observed concordance in concordant twin pairs	Observed discordance in discordant twin pairs
						years		
Siblings	136	27.9	22.5	24.3	—	—	—	—
Dizygotic cotwins	42	29.3	23.8	26.8	188	30.3	5.0	6.2
Monozygotic cotwins	48	26.5	23.9	25.3	30	30.9	3.5	5.7
Total number	226	27.8	23.1	24.8	218	30.4	4.2	6.1

they developed the disease, which means they were still in those age groups in which the general mortality rate of the female is also found to exceed that of the male.

A similar sex variation in morbidity reveals itself in the finding that the brothers and male twins of the index cases had a higher average age at disease onset than the sisters and female twins (table 9). This sex difference amounts to 5.4 years in the siblings and to 2.6 and 5.5 years, respectively, in the monozygotic and dizygotic twin groups, while the total age differences between the three sibship groups are only of limited extent. Statistically it is to be expected, of course, that the average age at disease onset will be somewhat lower in the siblings than in the twin partners of tuberculous index cases, since only the siblings have an equal chance of being older or younger at disease onset than the index cases.

It is also shown in table 9 that the variations in concordance between the two types of twins are not explainable on the basis of differences in the period of time during which the twin partners were under observation before they were classified

as concordant or discordant. The monozygotic as well as the dizygotic members of the discordant twin groups had already reached an average age of thirty-one years at the time of their examination for this survey, and both categories of cotwins had at that time been discordant for about six years since the development of tuberculosis in the index cases.

The distribution of the sibship morbidity rates according to fatal and nonfatal courses of the disease is demonstrated in table 10. In the sibling group, this table also takes into account the variations in morbidity and fatality rates according to race (white and nonwhite persons) and according to whether these persons are related to fatal or nonfatal index cases. This differentiation has been limited to the full siblings, since the corrected morbidity and fatality figures for the other sibship groups are not based on rates of reference which would safely allow several further subdivisions.

TABLE 10

Distribution of the sibship morbidity and fatality rates and their variations according to race and the course of disease in the index cases

	HALF-SIBLINGS	ALL FULL SIBLINGS	SIBLINGS OF ALL DECEASED TWINS			ALL COTWINS	
			White	Nonwhite	Total	Dizygotic	Monozygotic
Number of persons							
All fatal tuberculosis cases	2	72	20	8	28	22	23
Corrected rates of reference	33.5	534	185	35	220	164	55
Corrected rates (Weinberg method)							
Fatality	5.97	13.5	10.8	22.9	12.7	13.4	41.8
Nonfatal morbidity	5.97	12.0	13.9	3.4	12.6	12.2	45.5
Total corrected morbidity	11.9	25.5	24.6	26.3	25.2	25.6	87.3

The most interesting finding of this analysis is that there is no significant variation between white and nonwhite sibships with regard to their total morbidity figures. Fatal and nonfatal cases are about equally distributed in all the four sibship groups. The main effect of the racial factor reveals itself in a marked excess of fatal over nonfatal cases in the nonwhite group, which shows a fatality rate of 22.9 per cent as compared with 10.8 per cent for the white group. It may also be noted that the morbidity and fatality figures for those siblings who are related only to fatal index cases do not significantly differ from the respective rates for the total number of siblings.

Additional evidence against a simple correlation between closeness of blood relationship and increasing similarity in environment with correspondingly intensified opportunity for infection is obtained by an investigation of the distribution of exposed and nonexposed cotwins in the two groups of twins (table 11). This analysis reveals that 20.5 per cent of all monozygotic pairs are concordant without known exposure of the cotwins, while 56.1 per cent of all dizy-

gotic twin partners are discordant despite known exposure either to an index case or to another family member. One may also note that 61.5 per cent of the monozygotic pairs with nonexposed cotwins are concordant, although these twin partners had no history of known exposure, and that 73.7 per cent of the exposed dizygotic twin partners are discordant in spite of known exposure.

The significance of intimate contact may or may not find its adequate expression in the statistical differences from 69.2 to 61.5 per cent and from 73.7 to 87.3 per cent, respectively, as found with respect to exposure between the concordant twin partners of the monozygotic group and between the discordant twin partners of the dizygotic group. It may also be important in this connection that the increase in the rate of concordant cotwins due to the factor of exposure is greater in the dizygotic group (12.7 to 26.3 per cent)than in the monozygotic group (61.5 to 69.2 per cent). There can be no doubt, however, that any such

TABLE 11

Distribution of exposure in the concordant and discordant twin pairs

TYPE OF TWINS	COTWINS WITH KNOWN EXPOSURE					COTWINS WITHOUT KNOWN EXPOSURE					ALL COTWINS		
	All exposed cotwins	Concordant		Discordant		All non-exposed cotwins	Concordant		Discordant		Total number	Rate of cotwins in per cent	
		Number of persons	Per cent	Number of persons	Per cent		Number of persons	Per cent	Number of persons	Per cent		Concordant without exposure	Discordant with exposure
Monozygotic.....	52	36	69.2	16	30.8	26	16	61.5	10	38.5	78	20.5	20.5
Dizygotic..	175	46	26.3	129	73.7	55	7	12.7	48	87.3	230	3.0	56.1
Total number.....	227	82	36.1	145	63.9	81	23	28.4	58	71.6	308	7.5	47.1

variation in relation to exposure does not suffice to explain a ratio of 1:3.5, or 25.6:87.3 per cent, as has been obtained for the collective morbidity rates of dizygotic and monozygotic twin partners.

That a genetic mechanism modifies individual resistance to tuberculosis is demonstrated still more clearly if the similarities in extent and outcome of the disease are taken as additional criteria of comparison. This is the objective of table 12[8] which compares the cotwin groups with similar and dissimilar behavior (unsatisfactory and satisfactory resistance) to the disease, instead of comparing the twin groups with and without manifest tuberculosis as was done by the use of the concordance and discordance rates. The group designated as suf-

[8] The authors take pleasure in acknowledging the assistance rendered by Miss Jean Downes of the Milbank Memorial Fund and Dr. Joseph Zubin of the New York State Psychiatric Institute and Hospital in tabulating the material of tables 12 and 13. They also wish to express their appreciation of the generous help extended by Drs. Lowell J. Reed and Paul R. David of Johns Hopkins University, Department of Biostatistics, in the statistical analysis of the entire survey.

ficiently resistant includes the subgroups II and I, that is, the cotwins who developed either mild forms of tuberculosis with subsequent arrest of the disease or no tuberculosis at all in spite of definite exposure; while the insufficiently resistant group consists of the far advanced and fatal cases of tuberculosis as classified in the subgroups III and IV.

TABLE 12

Variations in resistance to tuberculosis as indicated by the differences in extent and course of the disease between the two members of twin pairs

CLASSIFICATION OF SIMILARITY IN BEHAVIOR TO TUBERCULOSIS	EXTENT AND COURSE OF TUBERCULOSIS IN TWIN PAIRS				NUMBER OF TWIN PAIRS	
	First member		Second member		Monozygotic	Dizygotic
	Clinical classification	Subgroup	Clinical classification	Subgroup		
Complete dissimilarity	Fatal	IV	No tuberculosis (exposure)	I	0	38
	Fatal	IV	No tuberculosis (no exposure)	Ia	0	7
Less complete dissimilarity	Fatal	IV	Minimal with arrest	II	1	16
	Advanced	III	No tuberculosis (exposure or no exposure)	I, Ia	8	86
Complete similarity	Minimal with arrest	II	Minimal with arrest	II	3	2
	Advanced	III	Advanced	III	8	3
	Fatal	IV	Fatal	IV	9	7
Less complete similarity	Minimal with arrest	II	No tuberculosis (exposure or no exposure)	I, Ia	22	57
	Advanced	III	Minimal	II	14	8
	Fatal	IV	Advanced	III	13	6
Total number of pairs						
All dissimilar pairs					9	147
All similar pairs					69	83
Grand total					78	230
Ratio						
No tuberculosis to fatal tuberculosis					0:78	1:4
Dissimilar resistance to similar resistance					2:16	2:1

In comparing dissimilarity and similarity in behavior to the disease, one obtains a ratio of 2:16 (9:69) in the monozygotic group, and a ratio of 2:1 (147:83) in the dizygotic group. In other words, similar behavior is about eight times more frequent than dissimilar behavior in monozygotic twins, but it is only one-half as frequent in dizygotic twin partners. Consequently, the difference in similarity of resistance between the two twin groups is expressed by a ratio of 1:16, which far exceeds the difference found in their original morbidity rates.

In fact, the chance of dying from tuberculosis is practically zero for a tuberculous patient who is the monozygotic twin of, or genetically identical with, a person who remains free of tuberculosis despite definite exposure to infection. However, the chance of dying is 1:4 if the person is merely the patient's sibling or dizygotic twin, which means that he is as likely to differ in the inherited elements for a satisfactory resistance as are two brothers or sisters.

Table 13 expresses the same data in rates rather than in ratios, classifying satisfactory resistance to tuberculosis according to (*1*) favorable and (*2*) very favorable forms of resistance. In the monozygotic group, about 12 out of 100 twin partners of tuberculous index cases showed favorable resistance and none showed very favorable resistance, if their cotwins were insufficiently resistant. In the dizygotic group, however, favorable resistance was seen in 64 out of 100

TABLE 13

Rates of satisfactory resistance to tuberculosis in the twin partners of tuberculous index cases

CLASSIFICATION OF SATISFACTORY RESISTANCE	TYPE OF TWINS	
	Monozygotic	Dizygotic
Total twins at risk	78	230
Favorable resistance of cotwins		
Number of pairs with complete and less complete dissimilarity in behavior to tuberculosis	9	147
Rate per 100 population	11.5	63.9
Very favorable resistance of cotwins		
Number of pairs with complete dissimilarity in behavior to tuberculosis	0	45
Rate per 100 population	0	19.5

twin partners of insufficiently resistant index cases, and very favorable resistance in about 20 out of 100 partners.

It may not be without significance that there is a considerable discrepancy between the ratio of 1:16 as found for the dissimilarities between the two groups of twins in the extent of their resistance to progressive disease, and the ratio of 1:3.5 as found for their differences in resistance to any form of clinical tuberculosis. This finding seems to be in line with the previously offered suggestion that the factors for resistance to the invasion of the tubercle bacillus and the factors for resistance to the spread of the established disease should not be assumed to be entirely identical with each other. In order to clarify this complex genetic problem more satisfactorily, however, it will be necessary to identify the morphological basis for the various constitutional mechanisms which have been shown in the present study to be capable of modifying susceptibility or resistance to tuberculosis.

Such an analysis in turn requires the evaluation of all the clinical and anthropometric data which will be discussed in the subsequent parts of this report.

Meanwhile, a number of general conclusions may be sufficient to summarize this first section of the inquiry into the heredoconstitutional variability of tuberculosis.

SUMMARY

1. An investigation of the possible significance of genetic factors in the development of tuberculosis was undertaken by means of the "Twin Family Method." This modification of the twin study method combines the technique of the original "twin method," that is, the comparison of unselected groups of one-egg and two-egg twin pairs, with the principles of a family study including the other sibship groups as well as the marriage partners of the twin index cases. The main objective of this procedure was to obtain for purposes of comparison a sufficient number of genetically dissimilar relationship groups reared under comparable environmental conditions.

2. The study was organized with the coöperation of the tuberculosis hospitals and clinics in the State and City of New York, which reported a total number of 657 twin cases within a period of about five years. The criteria for selection of the index cases were that they be born by multiple birth and that they had come under observation of one of the coöperating agencies with the diagnosis of tuberculosis.

3. The material used for analysis of the statistical data on manifest reinfection tuberculosis consists of 308 complete twin families with 616 twin partners, 930 full siblings, 74 half-siblings, 688 parents, and 226 marriage partners of twin patients. The random sampling of these 308 twin pairs is indicated by the proportion of 78 monozygotic to 230 dizygotic pairs, representing a ratio of about 1:3.

4. Consistency in the calculation of collective morbidity figures for the various sibship groups was obtained by the use of the Abridged Weinberg Method.

5. Comparison of the corrected morbidity rates reveals that the chance of developing tuberculosis increases in strict proportion to the degree of blood relationship to a tuberculous index case. The difference in morbidity between dizygotic and monozygotic twin partners amounts to a ratio of 1:3.5, their corrected concordance rates being 25.6 and 87.3 per cent, respectively.

6. The difference between the dizygotic and monozygotic cotwins increases to a ratio of 1:16, if the similarities in extent, course and eventual outcome of the disease are taken as additional criteria of comparison.

7. The consistent differences in tuberculosis morbidity among the various sibship groups of the twin index cases *cannot* be adequately explained on the basis of a simple correlation between closeness of blood relationship and increasing similarity in environment with correspondingly intensified opportunity for infection.

8. The analysis of the morbidity distribution in the sibship groups indicates that resistance to tuberculosis is modified by a heredoconstitutional mechanism which seems to be multifactorial in its genetic nature.

SUMARIO

1. Una investigación del posible significado de los factores genéticos en el desarrollo de la tuberculosis fué llevada a cabo por medio del "Método de la Familia Gemela". Esta modificación del método del estudio de gemelos combina la técnica primitiva, es decir, la comparación de grupos tomados al azar de pares de mellizos uni y bivitelinos con los principios de un estudio familiar que comprende los otros grupos gemelares, así como los cónyuges de los casos que figuran en el índice gemelar. El principal objetivo de este estudio fué obtener para fines de comparación un número suficiente de grupos genéticamente distintos, pero agrupados en un ambiente comparable.

2. El estudio fué organizado con la cooperación de los hospitales y clínicas de tuberculosis del Estado y Ciudad de Nueva York, que comunicaron un total de 657 casos de tuberculosis en gemelos en un período de unos cinco años. Las pautas observadas para seleccionar los casos que pasaron al índice, fueron haber nacido en nacimientos múltiples y haber sido observados por uno de los organismos cooperativos con el diagnóstico de tuberculosis.

3. El material utilizado para análisis de las estadísticas de tuberculosis de reinfección activa, comprende 308 familias gemelares completas con 616 cónyuges, 930 hijos de gemelos, 74 semigemelos, 688 padres, y 200 cónyuges de enfermos gemelos. La forma azarosa en que se obtuvo esa muestra de 308 pares de gemelos está indicada por la proporción de 78 monocigóticos por 230 pares bicigóticos, lo cual representa una ecuación aproximadamente de 1:3.

4. Se regularizó el cálculo de las estadísticas colectivas de morbidad para los varios grupos de parientes empleando la técnica aprobada de Weinberg.

5. La comparación de las estadísticas de morbidad corregida revela que las probabilidades de contraer tuberculosis aumentan en razón directa del parentesco a un caso de índice tuberculoso, equivaliendo la diferencia en morbidad entre los hermanos de los gemelos bicigóticos y monocigóticos a una proporción de 1:3.5, y representando los índices corregidos de concordancia 25.6 y 87.3 por ciento respectivamente.

6. La diferencia entre los co-gemelos bicigóticos y monocigóticos acrecienta a razón de 1:16, si se toman como pautas de comparación las semejanzas en extensión, evolución y desenlace final de la enfermedad.

7. Las constantes diferencias en morbidad tuberculosa entre los varios grupos comparados no pueden explicarse adecuadamente tomando por base la simple correlación entre el grupo de parentesco sanguíneo y la semejanza creciente en el ambiente con las correspondientes mayores oportunidades para infección.

8. El análisis de la distribución de la morbidad en los varios grupos emparentados en los casos del índice gemelar, indica que la resistencia a la tuberculosis se ve modificada por un mecanismo heredoorgánico en que parecen intervenir muchos factores con respecto a su naturaleza genética.

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DISCUSSION

Dr. Barbara S. Burks, New York, New York: This is a historic occasion, when the rôle of constitutional factors in tuberculosis has been clearly brought out at one of your national meetings. Doctor Kallmann has long been recognized for his energy and imagination in his work in human genetics, and he has presented you with some memorable data, as has Doctor Reisner in the illustrations just given.

There is an especially valuable feature of this study which we don't find in all twin studies which attempt to attack hereditary problems through the cotwin control method Doctor Kallmann has described to you. For there is often a bugbear in twin studies; we often find, with respect to environmental factors which may influence the development of a human trait, that identical twins have in effect a more similar environment than do the two-egg or fraternal twins. When that is so, particularly with respect to the development of certain social traits, we can't say for sure that the larger concordance between identical twins than between fraternal twins necessarily establishes a hereditary predisposition in the trait involved.

In this study, however, there is an important point: that the fraternal, or two-egg twins studied by Doctor Kallmann have a concordance which is the same as in ordinary siblings. Now, if the environment which twins usually have more similar than that of ordinary siblings had affected their relative susceptibility to the disease, we would expect to see fraternal twins more concordant than ordinary siblings. Though true that we might also expect to see identical twins more concordant than fraternal twins on the basis of environment alone (and we do so find them), the fact that the fraternal twins and the siblings have the same degree of concordance justifies us in assuming that the kind of factors within a family which make a family environment different for this child or *this* child are not influencing the results; the data thus seem to be crucial for showing the constitutional basis for tuberulcosis.

This does not discount the environmental factors which an organization like this one emphasizes. It doesn't discount codliver oil or tomato juice, or fresh air, or any of the other environmental factors which have undoubtedly been greatly responsible for reducing the tuberculosis death rate. There appears to be, however, a strong constitutional predisposition for the development of tuberculosis, for the degree of the intensity of the disease once it has been contracted, and for the prospects for recovery. This is shown by the monozygotic twins in Doctor Kallmann's and Doctor Reisner's study; when one twin not developing the disease has a cotwin who does develop the disease, the monozygotic or identical cotwin who does develop the disease has practically a 100 per cent chance of *not dying* of it. As a companion item of evidence to this, Doctor Kallmann has shown that, in fraternal twins if one twin does develop the disease, then 73 per cent of the cotwins do not develop the disease, even if exposed. In other words, when the relationship is not a complete genetic identity the chances for a cotwin not developing a disease even though exposed, are approximately three out of four.

Now, what does this mean to you, in terms of the resources that are available to you as practitioners? It means, if it is not possible to segregate a tuberculosis case in a hospital or sanatorium, it is at least advisable not to have the *nearest* relatives of the patient take care of him. The nearest relatives should be the ones most protected. The siblings and the offspring, if possible, might preferably go and live elsewhere during the course of the illness. It means that it is better to have a tuberculosis case taken care of by husband or wife than by parent, child, brother or sister. If it is necessary to have a relative take care of the patient, it is better to have a grandparent, uncle or aunt, or some other more remote relative responsible for immediate care.

There is another implication for the practitioner and for the public health administrator. Prophylaxis should begin in the regions where there is a history of heavy infection. There are certain areas where there is a heavy infestation of tuberculosis, for example, the long spine of the Appalachian Mountains. While there may be a considerable degree of truth to the fact that tuberculosis develops in such areas because of a heavy infestation which results in contagion, there is also the strong probability, as shown by this study, and by others that are confirmatory, that one reason for the heavy infestation in certain regions is a constitutional one.

Again with public health nurses who undertake work with tuberculosis patients, or with nurses who undertake tuberculous nursing in public or private hospitals, they should be selected, if possible, as being free from tuberculosis histories in their families. With the unusually heavy exposure that such nurses are subjected to, selected nurses will at least run a minimal chance of contracting the disease.

Finally, with your resources in the way of vitamins and other reinforcing elements of the diet that were described in a previous paper—if those are limited, as they usually are in any community for distribution to people who are economically marginal, they should be routed first of all to the families who need them most. That doesn't necessarily mean a household where there is an active case of tuberculosis, although it may mean that, but it means studying family histories, and using reinforcing items in the diet of those families where there is a past history of tuberculosis.

Dr. Max B. Lurie, Philadelphia, Pennsylvania: After the able discussion of this paper by Doctor Burks there is little that I can add. However, it would seem worth while to compare these studies on human beings with our experimental investigations on the natural resistance of rabbit families to tuberculosis. Briefly, six rabbit families which have been inbred brother to sister or parent to offspring for five to six successive generations without outbreeding and reared under absolutely identical environmental conditions throughout this time, show a resistance to tuberculosis which is characteristic for each family generation after inbred generation. The genetic constitution of the families *per se* determines whether, under given conditions of natural respiratory contagion to tuberculous cagemates, rabbits will acquire (*a*) a rapidly progressive primary generalized tuberculosis similar to the galloping disease of the South African Negroes, (*b*) a localized chronic ulcerative pulmonary phthisis analogous to the reinfection type of tuberculosis characteristic of white adults or (*c*) a disease of intermediate severity as seen in the American Negro. The fundamental variant in the disease developed by these several families was the degree of localization of the infection to the portal of entry. The family of very high resistance permitted little or no invasion of the disease by way of the lymph or blood stream. In the families of very low resistance these channels served for the rapid spread of the infection. In the families of intermediate resistance the lymphogenous and haematogenous dissemination was intermediate in extent. This limitation of the disease to the portal of entry was controlled by the rapidity and intensity with which the mononuclear cells at the point of invasion acquired local immunity to stem the growth and the dissemination of the parasite. The response of the tissues to the infection was determined by the genetic constitution of each family. Some of the trends of this investigation are now being exhibited at this meeting.

Now, Doctors Kallmann and Reisner have also shown similar differences in the progression of the disease in certain twins, which were also apparently controlled by their genetic constitution. However, there is one discrepancy between the results of the human and rabbit studies which requires some comment. In the twins the chief difference has been

one of rate of infection. In our rabbits the infection rate was not greatly different in the several families. About 60 to 80 per cent of each of the six families acquired tuberculosis. The attack rate in these families was therefore not conspicuously different. It was mainly the progression, type and chronicity of the disease which varied most constantly. As to the explanation of these apparent differences between our investigations on rabbits and those on human twins nothing can be said with certainty at the present time. The very high attack rate of our rabbits, 60 to 80 per cent per year, indicates that the intensity of exposure to the disease was inordinately greater than that operative in the twins. Perhaps, had these twins of different genetic constitution been exposed to the same amount of contagion as our rabbits, it is possible that the attack rate would not have been markedly different. The chief difference might then have been of essentially the same category as in our rabbits, namely, one of rapidity of progression of the disease.

Be that as it may, it is clear that much must be investigated before these questions can be answered. Still it is significant that such widely different studies as tuberculosis of human twins and the experimental disease in rabbit families have led to the same conclusions, namely, that individual resistance to tuberculosis is controlled by numerous hereditary constitutional factors.

Since the presentation of this discussion new data have been obtained on these rabbit families which closely correspond with the results of Doctors Kallmann and Reisner. When the intensity of exposure was greatly reduced, animals of great genetic resistance acquired an infection which healed completely, whereas a certain proportion of rabbits of very low genetic resistance simultaneously exposed to the same low contagion developed fatal tuberculosis.

ARTIFICIAL PNEUMOTHORAX IN NEGROES[1]

An Evaluation of the Results

REUBEN HOFFMAN

This paper reports the results of pneumothorax therapy employed in 358 Negro patients over a nine year period. In order to evaluate the results of pneumothorax therapy, an absolute distinction has been made between effective and ineffective pneumothorax, for only by the use of this distinction can conclusions be profitably drawn. The definition of effective pneumothorax is strictly limited to those cases in which there are sputum conversion, abatement of clinical symptoms and radiographic evidence of cavity closure.

MATERIAL AND RESULTS

The material upon which this report is based comprises 12 patients with minimal unilateral, 246 with moderately advanced (209 unilateral) and 100 with far advanced disease (47 unilateral). This classification, with age and sex distribution is shown in table 1.

TABLE 1

Showing age groups, sex and classification of tuberculosis in 358 pneumothorax cases

AGE	MALES			FEMALES		
	Minimal	Moderately advanced	Far advanced	Minimal	Moderately advanced	Far advanced
years						
0–10	1	1	2	0	1	1
11–20	1	21	8	7	61	24
21–30	0	45	20	1	55	26
31–40	1	26	7	0	21	7
41–50	0	7	1	0	5	2
50 and over	1	2	2	0	1	0
Total.....	4	102	40	8	144	60

A summary of table 2 shows that 313 unilateral and 45 bilateral pneumothoraces were induced in 358 patients. Adhesions were encountered in 90.5 per cent and prevented an effective collapse in 83.4 per cent. Of the 313 unilateral pneumothoraces, 43 (13.7 per cent) were effective *per se*, 109 (34.9 per cent) were rendered effective by closed pneumonolysis; 161 (51.4 per cent) were ineffective or remained ineffective after an incomplete pneumonolysis. Of the 45 bilateral pneumothoraces, 9 (20 per cent) were effective or rendered effective; 36 (80 per cent) were or remained ineffective.

[1] From the Maryland Tuberculosis Sanatorium (Colored Branch), Henryton, Maryland.

TABLE 2

Showing the results obtained in a total of 313 unilateral and 45 bilateral pneumothoraces

RESULTS	UNILATERAL		BILATERAL	
	Number	Per cent	Number	Per cent
Effective (by closed pneumonolysis)	109	34.9	5	11.1
Effective (no adhesions)	28	8.9	4	8.9
Effective (with adhesions)	15	4.8		
Total effective	152	48.6	9	20.0
Ineffective (no thoracoscopy)	131	41.8	32	71.1
Ineffective (incomplete pneumonolysis)	30	9.6	4	8.9
Total ineffective	161	51.4	36	80.0
Total pneumothoraces	313	100.0	45	100.0

TABLE 3

Comparison of the status at time of discharge of 152 effective and 161 ineffective unilateral pneumothoraces

	EFFECTIVE		INEFFECTIVE	
	Number	Per cent	Number	Per cent
To continue refills outside sanatorium	77	50.6		
Pneumothorax replaced with oleothorax	20	13.2		
Improvement after involuntary abandonment	10	6.6		
Improvement after voluntary abandonment	1	.7	32	19.9
Improvement after other collapse measures			23	14.3
Left without approval	10	6.6	20	12.4
Total discharges	118	77.7	75	46.6

TABLE 4

Comparison of the deaths in 152 effective and 161 ineffective unilateral pneumothoraces

	EFFECTIVE		INEFFECTIVE	
	Number	Per cent	Number	Per cent
Appearance or activation of contralateral disease	17	11.1	24	14.9
Extrapulmonary tuberculosis	8	5.2	2	1.2
Nontuberculous causes	3	2.0	2	1.2
Atelectasis	2	1.3		
Following other collapse procedures			8	5.1
Empyema	2	1.3	3	1.9
Spontaneous pneumothorax	1	.7	15	9.3
Progression after abandonment or premature loss	1	.7	32	19.8
Total deaths	34	22.3	86	53.4

A summary of tables 3 and 4 shows that, out of 152 effective unilateral pneumothoraces, 71.1 per cent were discharged, 6.6 per cent left without approval and 22.3 per cent died. Out of the 161 ineffective unilateral pneumothoraces, 34.2 per cent were discharged, 12.4 per cent left without approval and 53.4 per cent died.

The following tabulation records the status of 45 bilateral pneumothoraces at the time of discharge.

DISCHARGES	
To continue unilateral refills; other pneumothorax replaced with oil	2
To continue unilateral refills; other pneumothorax voluntarily abandoned	2
To continue bilateral refills outside sanatorium	1
One pneumothorax replaced with oil; other side obliterated spontaneously	1
Both pneumothoraces lost through spontaneous obliteration	1
Both pneumothoraces abandoned, followed by spontaneous improvement	1
Both pneumothoraces voluntarily abandoned	1
Left without approval	3
DEATHS	
Progression after abandonment of ineffective pneumothorax	33

A summary of the tabulation of the 45 bilateral pneumothoraces shows that 20.0 per cent were discharged, 6.7 per cent left without approval and 73.3 per cent died.

DISCUSSION

The origin of the adhesions, in most of the cases, is the localized pleuritis occurring during the first-infection phase of the disease. The involvement of the pleura during this phase is more common in Negroes than in whites, since Negroes suffer a much more severe first-infection lesion. A review of the films of 300 consecutive Negro children admitted to the sanatorium with first-infection tuberculosis showed that 10 per cent had effusions on admission or developed them while under observation. This incidence of effusions is more striking when it is known that 48 per cent of the children had X-ray and clinical evidence of active first-infection disease at time of admission, while in 52 per cent the disease was already inactive. How many of these 52 per cent had effusions during the active phase is unknown, but it is right to assume that the incidence of effusions during their phase of activity was no less than the observed incidence in the active group.

An additional factor explaining the high incidence of adhesions is the large number of extensive postprimary pneumonias (due to rupture of caseous nodes into bronchi) seen in these 300 films. It is right to assume that a large number of these pneumonias are responsible for the development of pleurisy by continuity.

These explanations for the origin of the adhesions have practical support by our observation that adhesions were commonly encountered in children when pneumothorax was induced for progressive primary lesions or early postprimary lesions.

The high incidence of adhesions (90.5 per cent) reported in this study is adequately accounted for when to the above offered causes are added, as additional

aetiological factors, the incidence of pleurisy occurring in the reinfection phase of the disease and pleural involvement by the haematogenous route.

Adhesions prevented an effective collapse in 83.4 per cent of the cases in this study. Tension cavities, an additional factor in preventing the achievement of an effective collapse, were encountered in 10 cases. Although these tension cavities were complicated by adhesions, they alone can be the cause, as was observed after successful severance of the adhesions in several of these cases.

An analysis of the patients' status at the time of discharge shows that the maintenance of an ineffective pneumothorax, due to adhesions, accomplishes little in the line of clinical arrest. The discharge rate in the effective group was 71.1 per cent, more than twice the rate in the ineffective group. The comparison of the discharge rate in the two groups is even more striking when it is taken into account that 14.3 per cent of the arrested cases in the ineffective group resulted from other surgical collapse procedures. If these cases in which an effective result was achieved by other collapse measures are omitted from the ineffective

TABLE 5

*Comparison of the incidence of complications forcing abandonment of pneumothorax in ineffective and effective groups**

COMPLICATION	INEFFECTIVE	EFFECTIVE
	per cent	*per cent*
Contralateral disease	18	12
Spontaneous pneumothorax	11	−1
Marked fluid formation	9	4
Obliterative pleurisy	7	2
Empyema	5	3
Obliteration (due to endobronchial lesions)	4	−1

* Note: not corrected for duplication.

group, the arrested cases in the two groups can then be compared on the basis of the results achieved by pneumothorax alone. Such a comparison gives 71.1 per cent arrested cases in the effective group and 19.9 per cent in the ineffective group, a ratio of 3.5:1.

The analysis also shows that unless pneumothorax is aided by some supplementary collapse procedure, it is markedly inadequate in the treatment of pulmonary tuberculosis. The only method, with very few exceptions, by which a pneumothorax can be made effective was found to be a closed intrapleural pneumonolysis. Since a pneumothorax can be recognized as ineffective early in the course of the therapy and, as a rule, will continue to be ineffective, delaying the pneumonolysis is time-wasting and dangerous. Time-wasting, because adhesions rarely stretch sufficiently to allow cavity closure and even if stretched will produce tension on diseased foci of the lung, which tension is aggravated by respiratory movements. Dangerous, because complications leading to abandonment or death will occur more often (table 5).

If a thoracoscopic examination shows that adhesions cannot be safely or satis-

factorily severed, either the pneumothorax should be supplemented by whatever additional collapse procedure is deemed advisable or promptly abandoned.

Complications: Table 5 shows the percentage incidence of complications occurring in the effective and ineffective groups.

Appearance or activation of contralateral disease occurred in 18 per cent of the cases in the ineffective group and in 12 per cent in the effective group. In 32 cases in both groups, bilateral disease was present at the time pneumothorax was induced and in 13 cases in both groups, the contralateral lesion appeared as a new involvement. Since 90 cases of bilateral disease were recorded, 58 contralateral lesions remained stationary or improved.

These figures reflect the ability of tuberculosis to spread in the Negro. The acute, exudative nature of many of these lesions, not uncommonly extensive from the beginning (responding hardly at all to collapse methods), and the rapidity with which they may pursue a fatal course, are also admittedly a characteristic of the Negro.

Obliterative pleurisy and fluid formation are grouped together because obliterative pleurisy is, in the main, the end-result of fluid formation; less often, the cause of fluid formation. The incidence of all effusions is not recorded in this study. Only those effusions are included which, because of their size and recurrence, caused ultimate abandonment of the pneumothorax. Together, these complications occurred in 16 per cent of the ineffective group and in 6 per cent of the effective group.

Many theories are advanced explaining the aetiology of effusions complicating pneumothorax. We believe that a small rupture of the lung at the site of the insertion of the adhesion, resulting in the formation of a small bronchopleural fistula, is one of the common causes for the occurrence of effusions in pneumothorax. These small fistulous openings are capable of rapid healing. There is little doubt, in our opinion, that some effective pneumothoraces are complicated by the presence of these small adhesions. These adhesions are very difficult to see on X-ray films, due to their proximity to adjacent tissues and also to respiratory movement of the adhesions, resulting in blurring. It is the rupture of the lung adjacent to these adhesions or the adhesions themselves that are believed to account for a significant percentage of the effusions occurring in pneumothorax.

Unless the amount of fluid was sizeable, it did not directly interfere with the maintenance of the collapse. Indirectly, even small effusions caused loss of the pneumothorax space by precipitating an obliterative pleurisy. The apposition or near apposition of a part of the lung to the chest wall, seen much more often in the presence of adhesions, with the intervening medium of fluid are the factors that set the stage for the obliteration. Inflammation of the visceral and parietal pleurae is the condition that precipitates the formation of granulation tissue which, by its subsequent contraction, results in the ultimate reëxpansion of the lung.

Of particular importance is the fact that spontaneous pneumothorax occurred in 11 per cent of the cases in the ineffective group, as contrasted with less than

1 per cent in the effective group, even though all pneumothoraces in both groups were maintained with subatmospheric pressures. That a spontaneous pneumothorax can complicate even a hypotensive pneumothorax is an argument against attempts to render an ineffective pneumothorax effective by the use of positive pressures. It is true, of course, that some spontaneous pneumothoraces occur through erosion of the lung by a tuberculous lesion, unrelated to adhesions or to the pressure of the pleural gas. But the great majority of spontaneous pneumothoraces complicating therapeutic pneumothorax are due to rupture of the lung at the site of the pulmonary insertion of adhesions.

Empyema occurred in 5 per cent of the ineffective cases and in 3 per cent of the effective cases. This incidence includes both the empyema that occurs suddenly, due to extensive or severe involvement of the pleura, characterized by signs of toxaemia, and the empyema that is the result of effusions having become progressively infected.

The complications encountered in bilateral pneumothorax in the effective group were two unilateral obliterative pleurisies and one unilateral massive fluid formation. The complications in the ineffective group were two unilateral spontaneous pneumothoraces, two unilateral empyemata, one bilateral effusion and one unilateral obliterative pleurisy. It is seen that a two and a half and three fold reduction in the incidence of complications occurred in the ineffective and effective groups, respectively. The comparison is of no undue significance, since the total number of unilateral pneumothoraces is three and a half times the number in the bilateral group. The explanation of this decreased incidence of complications, no doubt, lies in the fact that the patients for bilateral collapse therapy are more carefully chosen and that, whereas a unilateral pneumothorax may be carried for a somewhat longer time, pending decision as to the next step to be employed, a bilateral ineffective pneumothorax is promptly abandoned.

COMMENT

Of 358 cases, with no distinction made between effective and ineffective collapse, 48 per cent were discharged. This could mean that the results of pneumothorax therapy were unsatisfactory in more than half our cases. This undifferentiated result is, of course, not revealing. It indicates, however, that, if ineffective pneumothoraces are not rigidly excluded from any report dealing with this subject, an erroneous evaluation of pneumothorax therapy will result. Most of the reports on pneumothorax therapy in the literature do not stress this difference, many hardly mention it.

A review of all the admission films of the 358 cases in this study was followed by the definite opinion that, were the opportunity again presented to decide on the use of pneumothorax, it would be withheld in a rather large number of cases. Many of the massive, exudative lesions were the ones that were followed by spontaneous pneumothorax, massive fluid formation and contralateral spread. It can hardly be denied that some patients give every evidence of the fact that their tuberculosis will follow an uninterrupted, progressive course and that any collapse therapy used will be unavailing. These cases can be recognized with reasonable certainty and no collapse measures should be employed.

SUMMARY

An evaluation of pneumothorax therapy in the Negro is made, based on a nine year experience.

The material comprises 12 minimal, 246 moderately advanced and 100 far advanced cases of pulmonary tuberculosis. Out of this total of 358 cases in which pneumothorax was induced (including 45 bilateral), adhesions were encountered in 90.5 per cent and prevented the achievement of an effective collapse in 83.4 per cent.

Of the unilateral pneumothoraces 48.6 per cent were effective (all but 13.7 per cent following closed pneumonolysis); 51.4 per cent were ineffective or remained so after an incomplete pneumonolysis.

A comparison of the discharge rates between the effective and ineffective pneumothoraces shows that the rate is more than twice as high in the former.

A comparison of the complication rate in the ineffective and effective pneumothoraces shows that complications leading to abandonment or death occur more often in the former.

Unless a pneumothorax can be rendered effective (by closed pneumonolysis), it should be promptly abandoned.

SUMARIO

Constituye este trabajo una avaluación del neumotórax terapéutico en el negro, basada en nueve años de experimentación.

El material comprende 12 casos mínimos, 246 moderadamente avanzados y 100 casos avanzados de tuberculosis pulmonar. De ese total de 358 casos en que se aplicó el neumotórax (comprendiendo 45 bilaterales), se descubrieron en 90.5 por ciento adherencias que impidieron la obtención de un colapso efectivo en 83.4 por ciento.

Un 48.6% de los neumotóraces unilaterales obtuvieron éxito (todos menos 13.7% consecutivos a neumolisis cerradas); mientras que 51.4% no surtieron efecto o siguieron así tras una neumolisis incompleta.

Una comparación de las altas entre los neumotóraces eficaces e ineficaces reveló que el coeficiente es más del doble en los primeros.

Una comparación del índice de complicaciones en los neumotóraces eficaces e ineficaces, reveló que son más frecuentes en los últimos las complicaciones que conducen al abandono o a la muerte.

A menos que un neumotórax pueda covertirse en eficaz (por medio de una neumolisis), debe ser abandonado sin tardanza.

Acknowledgment is made to Dr. Otto C. Brantigan, Visiting Surgeon, for his skilful work with closed pneumonolysis and for the accurate descriptions of his observations in thoracoscopic examinations, which are the basis for some of the comments made in this paper.

LARYNGEAL TUBERCULOSIS IN THE NEGRO

DONALD F. PROCTOR[1,2]

During the past two years all patients admitted to the Henryton Tuberculosis Sanatorium have had a laryngeal examination and a special effort has been made to follow with repeated examinations all patients in whom any laryngeal lesion was found or suspected. This has been done not only to obtain facts about tuberculous laryngitis, but also to compile information that may lead to a better understanding of the various interrelationships between tuberculosis of the larynx and tuberculosis in its other manifestations.

Before the development of indirect laryngoscopy a true understanding of tuberculosis of the throat was impossible. Perhaps the best of the early papers on the subject was that of Trousseau and Belloc (1). They give a classical description of the signs and symptoms of laryngeal involvement, discuss the efforts of a century ago at visualization of the larynx and the methods of treatment then used. It is of interest to note that in 1839 the local treatment of tuberculosis of the larynx differed from to-day's only in the cauterizing agent. Until recently the early lesions of tuberculous laryngitis were practically unknown and cures of the disease were thought rare. St. Clair Thomson's (2) comprehensive study is one of the earliest thorough presentations of the subject. To-day many factors are still debated, such as the source of the infection, its incidence, its treatment, etc. Most of the differences of opinion can be traced either to the differences in material from which the figures are derived or to differences in the indications for laryngeal examination. If statistics are to be comparable they must be on sanatorium patients and on lesions found at routine examinations. Any other types of reports can only be of interest in respect to the special class of case they may represent.

This report (covering the period from November, 1940 to September, 1942) is based on the first 600 routine laryngeal examinations done at the Henryton Sanatorium, and the repeated examinations done on these patients through periods of at least six months and, in many cases, of over a year. The observations made are supplemented when necessary by material seen at the Mt. Wilson Sanatorium, the Baltimore City Hospitals and in private practice. However, all of the statistics presented are on the Henryton Sanatorium patients alone. These patients are all of the colored race. Fourteen per cent of the 600 patients had minimal pulmonary tuberculosis, 36 per cent moderately advanced and 49 per cent far advanced. A little more than 1 per cent of these patients proved subsequently to be nontuberculous. None of these patients was below the age of eleven years; 21 per cent were between eleven and twenty years of age; 45 per cent were between twenty-one and thirty years of age; 21 per cent were between thirty-one and forty; 9 per cent were between forty-one and fifty; 3 per cent

[1] Visiting Otolaryngologist and Bronchoscopist, Maryland Tuberculosis Sanatorium (Colored Branch), Dr. Reuben Hoffman, Superintendent, Henryton, Maryland.

[2] 6 East Eager Street, Baltimore, Maryland.

between fifty-one and sixty and 1 per cent as over the age of sixty. Forty-six per cent of the patients were females and 54 per cent males. About three-quarters of the women were below thirty and only half of the men were below this age.

A little less than one-third of all the patients showed a laryngeal lesion at some time during the period of this study, none of these in the nontuberculous group. Without biopsy (as a rule contraindicated in these patients) it is impossible to be certain about the tuberculous nature of some of these lesions. Oedema, hyperaemia and thickened mucous membrane are all observed in laryngeal disease other than tuberculosis. However hyperaemia localized in one part of the larynx, oedema or thickened mucous membrane limited to the posterior commissure and such other specific types of lesions are indicative of tuberculosis. Fortunately, from a diagnostic point of view, early malignant laryngeal tumors are almost always in the anterior third of the larynx, whereas almost invariably tuberculous lesions commence in the posterior third. In all but a very few cases one may be reasonably certain of the true tuberculous nature of the laryngeal disease. There can be little question that about 30 per cent of these 600 patients suffered from tuberculous laryngitis. Twenty-four per cent of all the laryngeal lesions (almost 8 per cent of the entire group) showed at some time during their course destruction of laryngeal tissue. No method was found to distinguish lesions of haematogenous origin from those resulting from direct infection through the epithelium. However, it seems very suggestive that no early lesions occur in the anterior portion of the larynx.

A CLASSIFICATION OF LESIONS

Observations on the appearance of tuberculous laryngitis as seen during this study are roughly in agreement with previous reports in the literature. However, a thorough understanding of the character of these lesions is of sufficient importance to warrant some reiteration. There are six principal characteristics in the appearance of tuberculous laryngeal lesions:

1: Hyperaemia.
2: Oedema.
3: Thickened mucous membrane.
4: Redundant mucous membrane and nodular outgrowths.
5: Superficial ulceration.
6: Destruction of the deeper laryngeal tissues.

Any one lesion may consist of one or more of these types and the more severe lesions always combine at least two. Actually, over half of the patients with laryngeal lesions fell simply into one of these groups and only about 10 per cent of the lesions were difficult to classify under one of the headings. It is not common to see marked hyperaemia or oedema in the presence of redundant mucous membrane or nodular outgrowths. Actual ulceration or deep destruction is always accompanied by hyperaemia but rarely by redundant mucous membrane.

EARLY LARYNGEAL TUBERCULOSIS

The earliest lesions invariably consist of a small area of either hyperaemia or pale thickened mucous membrane, usually in the posterior commissure or on one arytenoid. Almost without exception these lesions begin in the posterior portion of the larynx. Diffuse hyperaemia or pallor of the laryngeal mucous membrane without other abnormality is not indicative of tuberculosis.

Those lesions beginning with small localized hyperaemia sometimes clear completely in a few weeks; others go on to ulceration and still others to oedema, sometimes followed by ulceration. As a rule, these lesions are accompanied by some pain even in the early stages, but infrequently by hoarseness. When they go on to ulceration, especially when this is near the cricoarytenoid joint, there is usually intense pain and occasionally partial limitation of motion of the affected side. When healing takes place in this type of lesion, it is frequently complete with no residual deformity or hoarseness. Occasionally a rapid spread of the destructive process involves all of one side, or the entire posterior portion of the larynx and sometimes the epiglottis.

The lesions that begin with redundant or simply thickened mucous membrane are very slow in healing. Most commonly, this type undergoes a gradual increase in the amount of thickening or redundancy with a consequent irregular bulging of the posterior portion of the larynx. Most cases seem to remain in this condition definitely, while in others the bulging continues and spreads until an irregular nodular pale tumor lines the entire glottis. If ulceration or destruction accompanies this type of lesion (as it rarely does) it usually appears only after the arytenoids or false cords have been involved; when ulceration does occur the lesion follows a more benign course than other destructive types; but when healing occurs there is a more severe and permanent deformity. Laryngeal lesions characterized by this thickening of the mucous membrane are, as a rule, asymptomatic at first, and even in their worst forms are accompanied by little or no pain, although often marked hoarseness results from the mechanical effects of the tumor formed.

About one-eighth of these laryngeal lesions showed oedema early in their course. This almost invariably occurred over the anterior portion of one arytenoid, but occasionally over the posterior commissure, and sometimes involved almost at its onset the entire posterior portion of the larynx. The oedema appears tense, shiny, swollen, pale, bright pink in color in the presence of a very marked cellular infiltration and an acute inflammatory process. These patients usually suffer intense pain and severe hoarseness. If the oedema consists of a pale, boggy swelling of the tissues, the larynx never grows worse and the patient suffers little or no inconvenience. Larynges with the inflammatory type of oedema often heal rapidly, but occasionally, just as rapidly, will break down into the severe destructive type of lesion.

ADVANCED LARYNGEAL TUBERCULOSIS

In any sanatorium one is bound to find some lesions severe when first seen. Commonly, these patients show oedema of the inflammatory type in the posterior portion of the larynx, the epiglottis red and thick with a granular, unhealthy

mucous membrane, often showing small areas of ulceration. In these cases the larynx is usually nearly full of purulent sputum and an adequate view of the interior of the larynx is not obtained. This type of patient is always extremely hoarse and more often than not suffers a great deal of pain. The majority of these larynges grow progressively worse until the patient's death, often only a matter of days or weeks. However, we have observed 9 very severe lesions undergo remarkable healing, 7 in the face of a general downhill course, 2 in patients who died. When they do heal they invariably are left with marked deformity from scar tissue and destruction of cartilage. Other advanced lesions consist of extensive, pale, nodular thickening of the mucous membrane, sometimes the lumen of the glottis decreasing by as much as 70 or 80 per cent. This type of lesion is relatively stationary over long periods of time.

SYMPTOMS

It is often surprising to see a laryngeal lesion with ulceration and destruction with no pain; and it is sometimes remarkable to see how much disease there can be in the posterior portion of the larynx without producing hoarseness. Many patients who have neither pain nor hoarseness complain of persistent dryness or rawness or an annoying tickling sensation in the throat. When the patient does have pain it is almost always associated with referred pain in the ear (sensory fibres to the larynx and part of the external ear both passing through the vagus). At times, pain in the ear is the only symptom of which the patient complains. This pain is always worse on swallowing, often completely absent except when coughing or swallowing. If one remembers that the pain is one of muscle spasm and the hoarseness is simply a mechanical effect, it is easy to understand these variable symptom complexes.

Many patients with tuberculosis of the larynx have no complaints referable to the throat and speak with a clear voice. Forty per cent of these patients with laryngeal lesions denied any pain or hoarseness. From this it may be seen that not even by routine examination of all admissions to the sanatorium will all tuberculous lesions of the larynx be discovered, as some will develop after an original negative examination and present no symptom occasioning a repeat examination. Pain seems to be more uncommon in tuberculosis of the larynx in colored patients than in white patients. This is probably not attributable to the uncomplaining nature of the race, but is due to an essential difference in the type of lesion. Although this has not as yet been fully proven, probably the nodular outgrowths and chronic thickening of the mucous membrane are more prominent characteristics of laryngeal tuberculosis in the Negro than in the white.

CORRELATION WITH GENERAL FACTORS

The patients with laryngeal disease have been analyzed according to the following factors:

1: The predominant character of the laryngeal lesion.
2: The age and sex of the patient.
3: The course of the patient.
4: Extent of the pulmonary disease.
5: Course of the laryngeal lesion.

The results of this analysis are presented in tables 1 and 2. The salient points seem to be the following:

(*1*) Of all the laryngeal lesions reported here, the predominant characteristic in 41 per cent of the patients was hyperaemia, in 24 per cent thickened mucous membrane, in 14 per cent oedema, in 10 per cent superficial ulceration, in 7 per cent a pale, nodular thickening of the mucous membrane and destruction of the

TABLE 1

ALL PATIENTS	WITH LARYNGEAL LESION		WITHOUT LARYNGEAL LESION		TOTAL GROUP—600* PER CENT
	Number, 195	Per cent, 32.5	Number, 398	Per cent, 66.5	
Pulmonary lesion					
Minimal	11	6	75	19	14
Moderately advanced	51	26	163	41	36
Far advanced	133	68	160	40	50
Wassermann					
Negative	130	67	286	69	69
Positive	65	33	112	31	31
Sputum					
Positive	152	78	204	51	60
Negative	21	11	104	26	20
Changing	22	11	90	23	19
Fever					
None or low	62	32	230	57	50
Moderate	45	23	78	20	21
High	88	45	90	23	29
Course					
Satisfactory	60	31	228	57	49
Unsatisfactory	57	29	76	19	22
Died	78	40	94	24	29
Sex					
Male	98	50	223	56	54
Female	97	50	175	44	46
Age					
Below 20	31	16	90	23	20
20–30	90	46	169	42	44
Above 30	74	38	139	35	36

* Of this total group, 7, or 1 per cent, were nontuberculous.

deeper tissues in 4 per cent. Over 20 per cent of the patients showed a combination of these lesions.

(*2*) Sixteen per cent of all the patients with laryngeal lesions were below the age of twenty, 46 per cent between twenty and thirty, and 37 per cent over the age of thirty. Half were males and half females. Most of the lesions in patients below the age of twenty were in females and above thirty in males; but this was only of apparent significance, since the female patients were considerably younger on the average than the males.

(*3*) Thirty-one per cent of the patients with laryngeal lesions improved or grew

TABLE 2

Grouping of laryngeal lesions by types

INCIDENCE AND GENERAL COURSE OF LARYNGEAL LESIONS BY TYPES					SUBDIVISION ACCORDING TO (IN PER CENT):										
					Age			Sex		Course			Pulmonary disease		
Number	Per cent	Type	Course	Per cent	Below 20	20–30	Above 30	Male	Female	Improved	Unsatisfactory	Died	Minimal	Moderately advanced	Far advanced
		Hyperaemia	Worse*	15	37	6	9	20	15	0	17	28	0	18	15
			No change	57	45	59	62	60	48	52	55	60	67	46	60
			Better	28	18	35	29	20	37	48	28	12	33	36	25
79	40				29	44	27	50	50	35	23	41	4	29	67
		Oedema	Worse	19	0	0	26	8	9	0	23	29	0	13	27
			No change	19	0	50	10	31	27	33	0	42	50	0	27
			Better	62	100	50	64	61	64	67	77	29	50	87	46
27	14				4	23	73	54	46	23	50	27	8	31	58
		Thickened mucous membrane	Worse	13	0	14	12	21	4	0	8	31	0	0	22
			No change	61	50	61	63	42	71	64	61	56	100	53	60
			Better	26	50	25	25	37	25	36	31	13	0	47	18
47	24				4	61	35	46	54	37	28	35	9	32	58
		Pale nodular thickening	Worse	7	0	0	17	0	20	0	0	17	0	0	9
			No change	43	0	57	33	50	50	40	67	33	0	33	45
			Better	50	100	43	50	50	30	60	33	50	0	67	46
15	8				7	50	43	55	45	36	21	43	0	21	79
		Ulceration	Worse	33	50	30	25	20	35	0	0	50	0	100	33
			No change	45	25	50	50	40	50	50	50	42	0	0	53
			Better	22	25	20	25	40	15	50	50	8	100	0	14
19	10				22	56	22	42	58	22	11	67	11	6	83
		Destruction	Worse	25	0	50	16	20	0	0	20	33	0	0	28
			No change	38	0	0	51	60	0	0	40	34	0	0	44
			Better	37	0	50	33	40	0	0	40	33	0	100	28
8	4				0	25	75	100	0	0	62	38	0	13	87
		Average totals entire group and subdivisions	Worse	17	33	11	17	17	14	0	15	31	0	12	20
			No change	50	40	57	44	50	53	53	43	52	64	38	54
			Better	33	27	32	39	33	33	47	42	17	36	50	26
195	100				16	46	38	50	50	31	29	40	6	26	68

* Refers to course of laryngeal lesion.

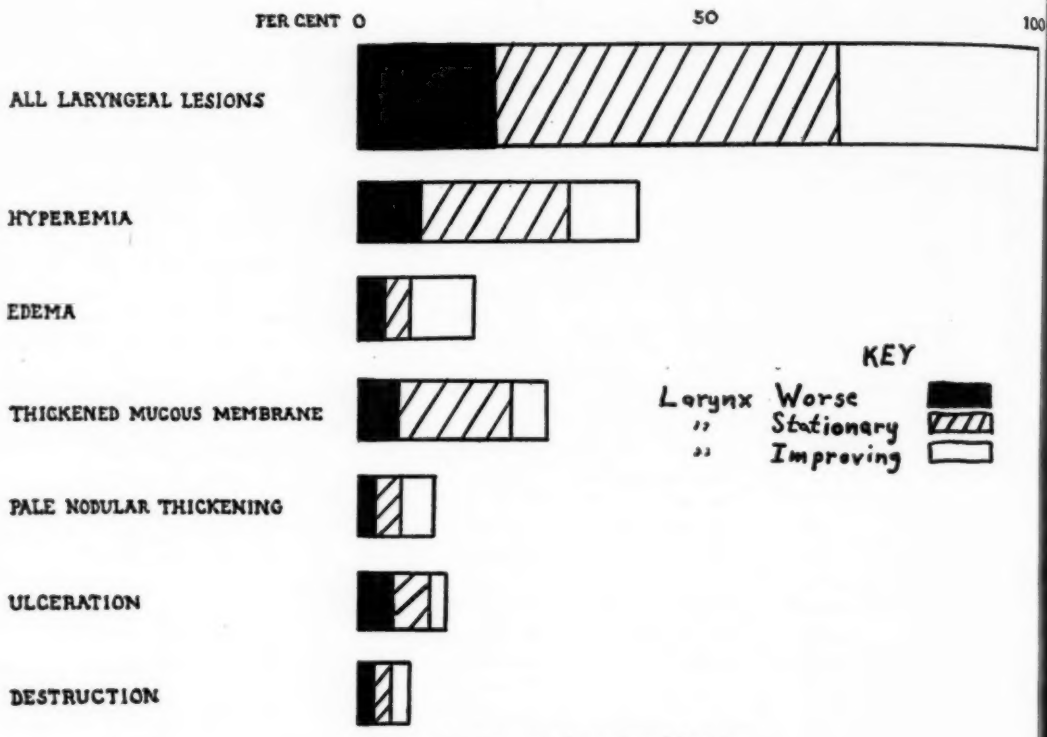

CHART 1. Course of laryngeal lesions

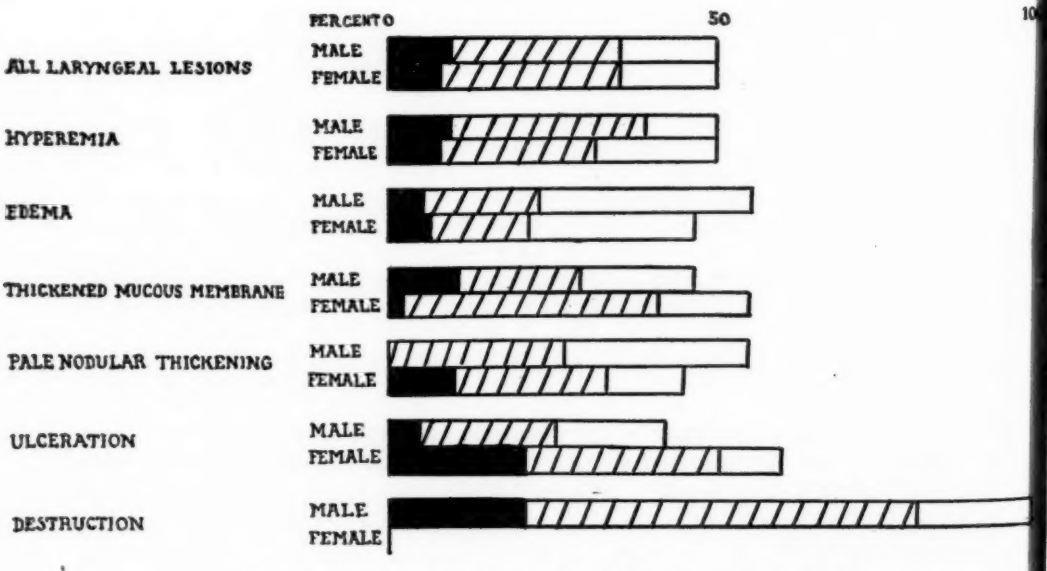

CHART 2. General course of laryngeal lesions grouped by sex

well during the time of observation; 29 per cent ran an unsatisfactory course; and 40 per cent died.

(*4*) Only 6 per cent of the patients with laryngeal lesions were admitted with minimal pulmonary disease; 28 per cent had moderately advanced disease; and 67 per cent far advanced.

(*5*) Seventeen per cent of the laryngeal lesions grew worse during observation; 33 per cent improved or grew well; and 49 per cent failed to undergo any radical

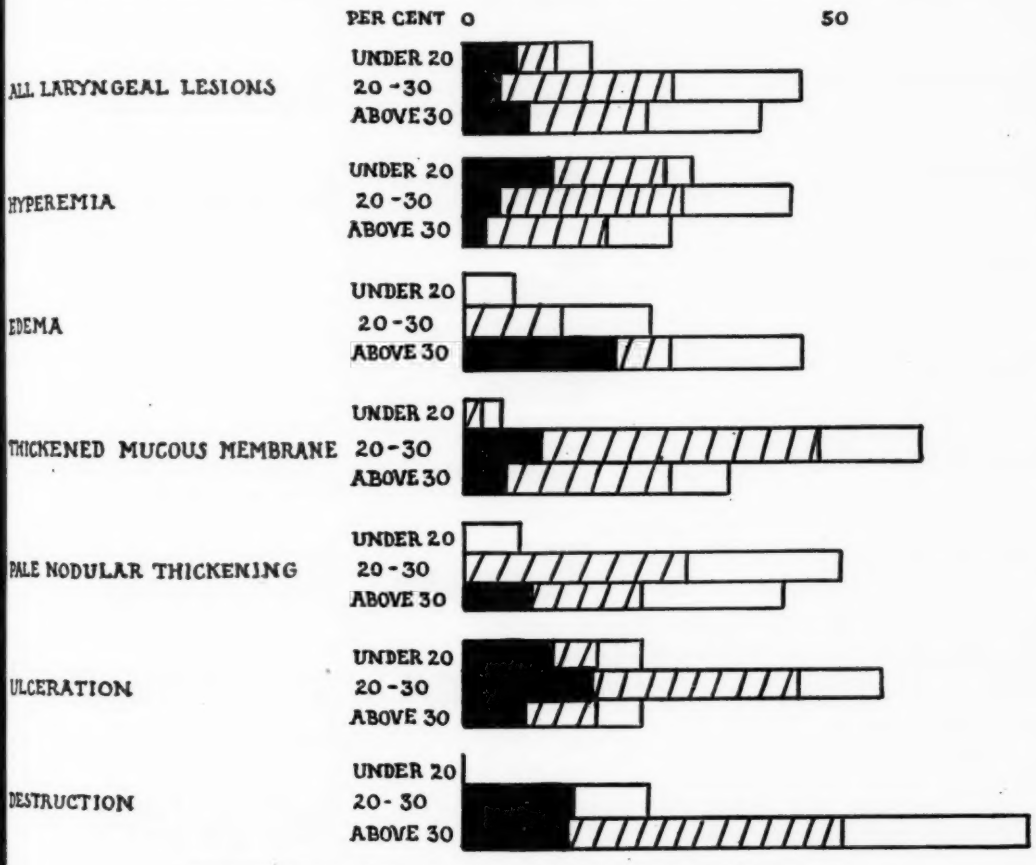

CHART 3. General course of laryngeal lesions grouped by age

change. Many of the larynges in the latter group probably improved and very few grew worse, as any increase in the symptoms invariably occasioned a repeat examination. It is interesting to note that although the classification as to course of laryngeal lesions differs from Myerson's (3), in this group the percentage of lesions improving (33 per cent) was almost twice the number quoted by him as growing well (17 per cent).

(*6*) The laryngeal lesions predominantly characterized by oedema had by far the best prognosis. This was particularly true of patients below the age of

thirty. The females had a somewhat better prognosis as to the laryngeal lesion than the males, particularly between the ages of twenty and thirty years.

(*7*) The worst prognosis in regard to the larynx was in lesions characterized by superficial ulceration. This was so in all age groups, but particularly so in females below the age of twenty. Where there was destruction of the deeper tissues the prognosis (for the laryngeal lesion) was particularly bad in males between twenty and thirty.

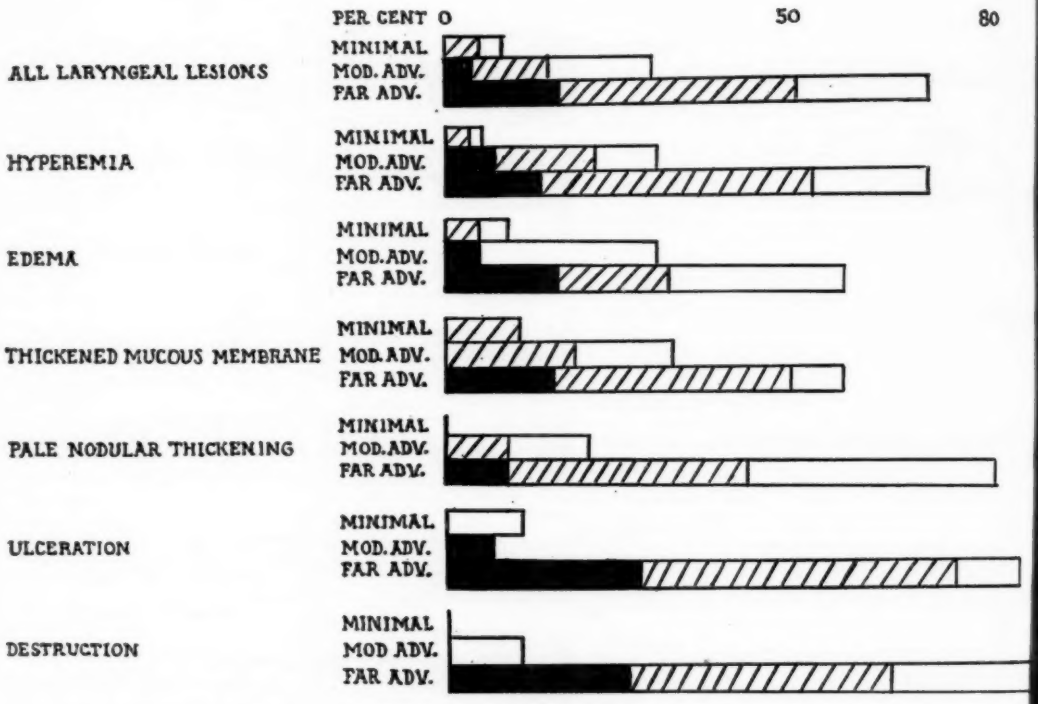

CHART 4. General course of laryngeal lesions grouped by extent of pulmonary disease

(*8*) The worst prognostic factor was the youth of the patient. Thirty-three per cent of all the laryngeal lesions in patients below twenty grew worse under observation.

(*9*) In patients who were generally improving, almost half of all the laryngeal lesions improved and not one grew worse. Not a single laryngeal lesion grew worse in patients with minimal pulmonary disease.

(*10*) In patients over the age of thirty, destructive or oedematous laryngeal lesions occurred relatively most commonly. Between twenty and thirty there was a relative preponderance of chronic thickening of the mucous membrane and, below twenty, of hyperaemia or superficial ulceration.

From all of this it is apparent that (at least in colored patients of this class) there are distinct types of laryngeal tuberculosis and that these types have char-

acteristics which are fairly predictable. Thus, on finding laryngeal tuberculosis, it is not enough to simply note its presence and degree. The character of the laryngeal lesion and the associated general factors must be noted and conclusions may be drawn.

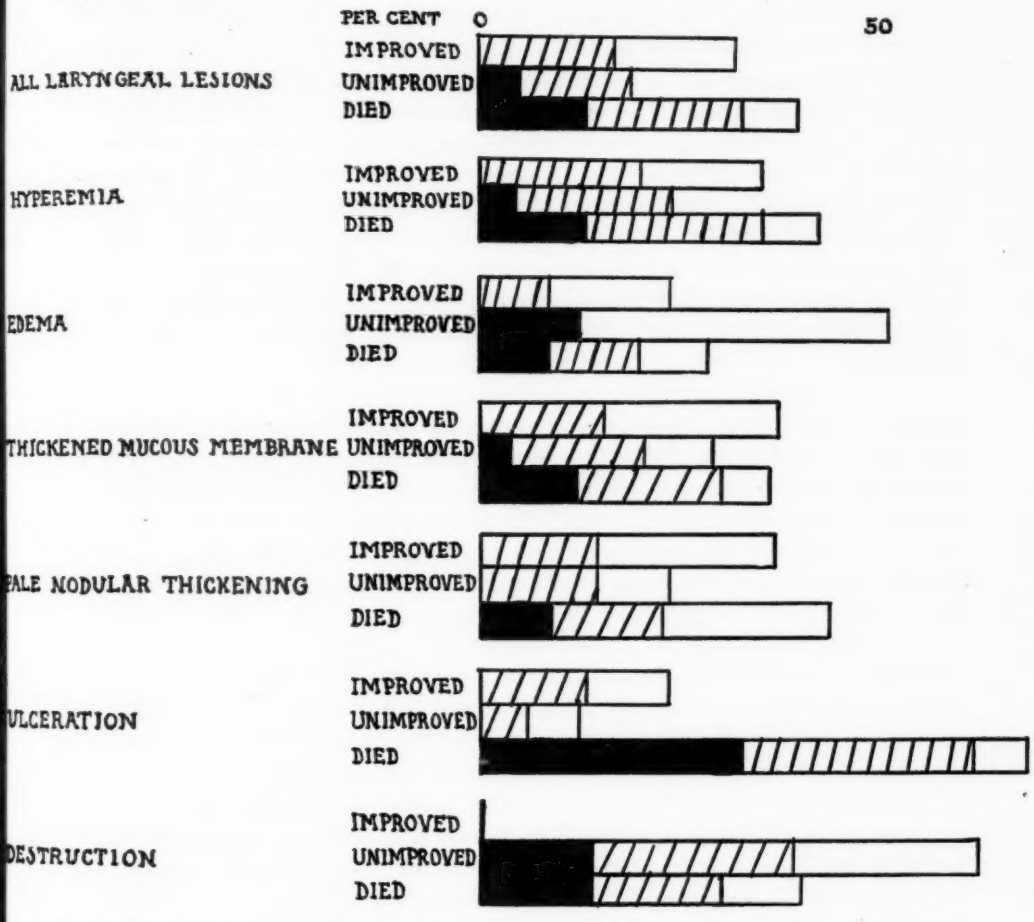

CHART 5. General course of laryngeal lesions grouped by course of pulmonary disease

PROGNOSIS OF LARYNGEAL TUBERCULOSIS

If a twenty year old patient has an oedematous arytenoid with acute inflammation about it, pain and hoarseness, the larynx will get well. If the same lesion occurs in a patient over thirty, particularly if the general course is unsatisfactory or if the lung disease is far advanced, there is about one chance in four of that larynx growing worse, and particular care must be taken to avoid this. If the oedema is pale and flaccid the lesion will never grow worse and no especial care need be taken.

If an eighteen year old patient has a small area of brilliant hyperaemia over one

arytenoid, there is cause for worry. Every effort must be made to prevent progression of this lesion. If the patient has minimal tuberculosis or if the condition is generally improving, it is certain that the larynx will grow well; but if the condition is growing worse the larynx is likely to ulcerate or even break down extensively in a short period of time. If the same lesion occurs in a patient over the age of twenty there is much less cause for apprehension. A brilliant hyperaemia in the presence of any tuberculous laryngeal lesion is in general a bad sign.

Ulcerative laryngeal lesions will almost certainly not heal if the pulmonary lesion is not arrested; but once the pulmonary lesion is improving or arrested, fears for the larynx are at an end. In patients with minimal tuberculosis, superficial ulcerations of the larynx need cause no worry as to the eventual outcome.

Larynges with thickened mucous membrane or pale, nodular tumors will not grow worse unless there is far advanced pulmonary disease, and even then are unlikely to grow worse if the patient is below thirty. These larynges are likely to remain stationary over long periods of time and this need not be a cause for apprehension.

Table 1 shows a comparison of various factors in the group with laryngeal lesions and the group without this complication. The most outstanding fact is that 69 per cent of the patients with laryngeal lesions either died during observation, or were running an unsatisfactory course at the conclusion of the period of this report, compared to 51 per cent in those without laryngeal complications. This fits in with the fact that the laryngeal lesions were relatively more common in patients with moderately or far advanced pulmonary disease.

TREATMENT

During the period of this report there has been no local treatment of laryngeal tuberculosis at the Henryton Sanatorium, except voice rest. In view of this, it is interesting to emphasize the fact that the percentage of laryngeal lesions reported cured in this study is as good as or better than is the case where cauterization and other types of laryngeal therapy are used. It is also worth noting that about 7 per cent of the laryngeal lesions steadily improved while the patient was dying and that in about 10 per cent the laryngeal lesion remained stationary while the general course improved. This is not evidence that the status of the pulmonary lesion is of no importance in relation to the laryngeal lesion, for such is not at all the case. However, it should emphasize the fact that laryngeal tuberculosis must not only be studied in its relation to general tuberculosis, but also as an entity itself.

I have had a limited opportunity to observe results from the use of galvanocautery in other hands and have carefully examined various reports in the literature on this type of therapy. There is no definite proof that this is an effective treatment in laryngeal tuberculosis, and even in the best of hands it may be harmful. It seems an illogical form of therapy in laryngeal disease. In the nonulcerated lesions there is the risk of producing ulcers, and where there is ulceration without deep destruction, necrosis, scarring and permanent deformity may result. In the presence of extensive destruction there is invariably an

acutely inflamed process and there can be little doubt that with the greatest of care an increase in this inflammation will result.

If these things are true of the treatment of laryngeal tuberculosis, why is it so widely accepted that cauterization of endobronchial tuberculosis with strong solutions of silver nitrate is of benefit? Silver nitrate has a far more superficial effect on the tissues than the galvanocautery. The actual cautery in this respect is more like silver nitrate than the galvanocautery. The larynx is peculiarly susceptible to unfavorable reactions to irritants, its tissues being very liable to become markedly oedematous and to ulcerate on relatively slight provocation. This is due in part to the tremendous degree of activity of the entire larynx at all times, even when at voice rest, especially in a patient subject to chronic cough. The mere act of respiration is associated with motion in the larynx, and coughing, swallowing, sneezing or speaking, all call for violent motion on the part of the laryngeal muscles. Anyone who has ever had a painfully sore throat can bear witness to this. As a result of this, any treatment of the larynx must be soothing, restful and must avoid trauma to the laryngeal tissues if it is to do more good than harm.

Actually, the more enthusiastic proponents of cauterization of the larynx advise its use only in a small number of carefully selected patients, and this study indicates that this is the group of patients whose larynges will often heal with no therapy but voice rest. Unless similar laryngeal lesions in similar patients are treated, the efficacy of cauterization and vocal rest cannot be compared.

I would like to emphasize the well known facts in regard to voice rest. It is of absolutely no use to warn the patient to rest his voice and let it go at that. The motion of laryngeal muscles on whispering is nearly as great as on normal phonation. There must be absolutely no use of the larynx for purposes of speech. Paper and pencil must be constantly with the patient and it must be his sole means of communication.

The most successful therapeutic program in laryngeal tuberculosis at present is:

(*1*) Persistent search must be made for the early laryngeal lesions.

(*2*) Complete voice rest must be strictly enforced as soon as a laryngeal lesion is suspected and maintained until the lesion has healed or reached a stationary condition.

(*3*) No words should be minced in warning the patients of the dire consequences of neglecting a laryngeal lesion.

(*4*) Tracheotomy of course may be resorted to when respiration is interfered with by the extent of the lesion. A fair trial should be given this method of treatment in the far advanced laryngeal lesions with extensive destruction. The fear of a tuberculous fistula in the neck seems unwarranted, especially when compared to the desirability of eliminating a destructive laryngeal lesion. It certainly offers the most effective method of putting the larynx at rest.

(*5*) When pain is sufficient to interfere with sleep or nutrition there should be no hesitation about injection of the superior laryngeal nerve. This is a simple procedure which anyone can do. Usually injection of one nerve suffices, but both nerves may be injected, and repeatedly injected, without fear of any untoward

reaction. If one injection fails to stop the pain for more than a few days, repeated injections are usually less successful. Patients whose pain is intractable after injection (particularly if relief is obtained for a short time) should have section or crushing of the nerve on direct exposure. Complete section or crushing should not be done bilaterally as there is too much interference with swallowing.

(*6*) Regardless of what else is done, there must be voice rest and no trauma!

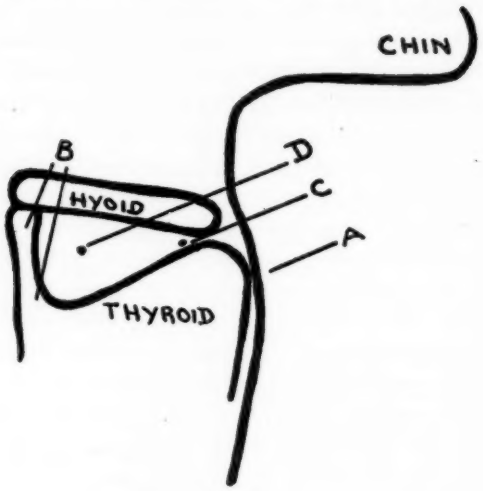

FIG. 1

Injection of the superior laryngeal nerve is simple enough to be tried (successfully in most cases) by any physician (figure 1).

1: The operator's hands are cleaned thoroughly and the patient's neck painted with any desired antiseptic.

2: Just to the side of the Adam's apple (A), the anterior portion of the thyrohyoid triangle is located.

3: A small wheal is made in the skin just posterior to this point (C) with novocaine.

4: A finger is held firmly in the posterior portion of this triangle (B) holding the carotid sheath back.

5: A long needle (attached to syringe holding 1 cc. of 70 per cent alcohol) is inserted through the wheal at C and aimed at the point D.

6: Holding the finger firmly and steadily at B the point of the needle systematically explores the posterior portion of the triangle until the patient suffers a sharp pain in the ear.

7: A few drops of the alcohol are injected. If the patient coughs the needle is withdrawn about a millimeter and the rest of the alcohol is injected. If there is no cough the full cubic centimeter is injected immediately.

8: If the procedure is successful the patient should immediately be able to drink water with considerably less, or no pain.

As yet there is no evidence that the pathology of any particular lesion is a clue to the pathology of the disease in other parts of the body, and probably there is no

constant relationship between them. However, the pathology of each laryngeal lesion as evidenced by its physical appearance, combined with the general factors, is a definite clue to the future course of each case of laryngeal tuberculosis.

SUMMARY

1. In routine laryngeal examinations on 600 consecutive admissions of colored patients, 195 tuberculous laryngeal lesions were found.

2. During periods of from six to twenty months, one-third of these lesions healed or markedly improved and about one-sixth grew progressively worse.

3. When these lesions were divided into groups according to certain distinct characteristics in their appearance, certain consistent factors were found in regard to course and prognosis.

4. Voice rest was found to be at least as effective a method of therapy as any other now in general use.

SUMARIO

1. En los exámenes laríngeos de 600 casos consecutivos de enfermos de color, se descubrieron 195 lesiones tuberculosas de la laringe.

2. Durante períodos que variaron de 6 a 20 meses, la tercera parte de esas lesiones cicatrizaron o mejoraron decididamente y aproximadamente la sexta parte continuaron agravándose.

3. Al dividir dichas lesiones en grupos, conforme a ciertas características de su aspecto, se descubrieron ciertos factores consistentes en cuanto a evolución y pronóstico.

4. El reposo de la voz resultó ser un método terapéutico por lo menos tan eficaz como cualquier otro empleado hoy día generalmente.

I wish to express my appreciation to the entire staff at the Henryton Sanatorium (particularly to Dr. Reuben Hoffman, Superintendent) for their coöperation and assistance in the work reported in this paper.

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THE SURGICAL RELIEF OF PAIN IN TUBERCULOUS LARYNGITIS[1]

OTTO C. BRANTIGAN AND REUBEN HOFFMAN

Severe pain, associated with an ulcerative tuberculous laryngitis, seriously interfering with nutrition and rest, has occurred in a small percentage of our patients. Its infrequence, however, in no way lessens the problem it presents. Pain has been so severe that patients refused to eat and starvation hastened the end.

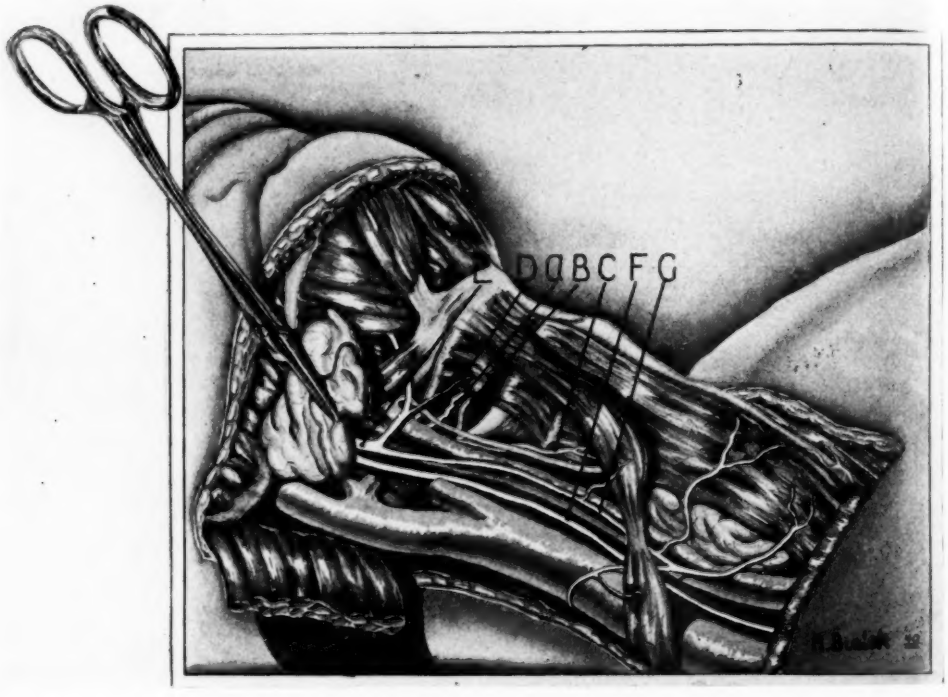

FIG. 1. Drawing made from a dissection of a cadaver to illustrate the anatomy of the operative field.

A, internal branch superior laryngeal n.; B, laryngeal branch of superior thyroid a.; C, external branch superior laryngeal n.; D, thyrohyoid branch of hypoglossal n.; E, hypoglossal n.; F, vagus n.; G, descending hypoglossal n.

In the majority of cases the injection of the internal branch of the superior laryngeal nerve with 70 per cent alcohol has been satisfactory. In some, either the relief from pain was ineffectual or repeated injections were necessary. It has been observed that, when the first injection of the nerve was followed by partial relief or by relief for only a short time, the results from subsequent injections were even less satisfactory.

[1] From the Maryland Tuberculosis Sanatorium (Colored Branch), Henryton, Maryland.

To insure certain and lasting relief in these cases, surgical interruption was resorted to. Complete division of the internal laryngeal nerve on one side was not followed by sufficient relief of pain in cases where there was extensive ulcerative laryngeal disease. Complete division of the nerve on both sides (one case) relieved pain, but was followed by excessive aspiration of food and water. It was then found that simultaneous, bilateral, *partial* section of the internal laryngeal nerve was followed by complete relief of pain and the aspiration of food was not greater than before the operation.

The operation is performed under local infiltration anaesthesia. A vertical incision, approximately one inch long, is made one inch lateral to the mid-line of the neck over the area delineated by the hyoid bone and the thyroid cartilage. The incision is carried through the cervical fascia to the omohyoid muscle and then along the superficial surface of this muscle and the thyro-hyoid muscle at whose posterior border the hyothyroid membrane is found. The internal laryngeal branch of the superior laryngeal nerve runs superficial to this membrane for a short distance before piercing it. It should be pointed out that the laryngeal branch of the superior thyroid artery is always found *superficial* to the internal laryngeal nerve. Approximately seven-eights of the nerve is cut through with a small pair of eye scissors.

The bilateral partial section has been performed on 10 patients and the relief from pain was immediate and lasting. No unusual aspiration of food or liquids was observed. If aspiration of food or liquids was present before the operation, due to extensive destruction interfering with glottic closure, the aspiration will persist after the operation. The bilateral operation is tolerated by extremely ill patients.

Aside from its mere palliative value, the procedure has an important therapeutic indication. This is in the individual whose pulmonary lesion is amenable to improvement (either by surgery or spontaneously), but whose unfavorable course is started and furthered by the impairment in nutrition and lack of rest due to a painful laryngeal lesion. A significant number of ulcerative laryngeal lesions have been observed to heal even in the face of a progressive pulmonary lesion. Where the pulmonary lesion is stationary, then every effort should be made to control the pain of the laryngeal lesion. If injection fails to bring about relief promptly, bilateral partial section should be carried out.

CLINICAL MANAGEMENT OF INTESTINAL TUBERCULOSIS[1]

WILLIAM M. PECK[2] AND JULIA M. JONES[3]

With the assistance of Mary Grieve Jacobson, Dietitian

McConkey and Smith (1, 2, 3) have previously called attention to the experimental production of intestinal tuberculosis in vitamin C deficient guinea pigs. Clinical application of this principle led to the impression that adequate dosage of codliver oil with tomato juice is effective in the prevention and treatment of intestinal tuberculosis. The present study was undertaken in an effort to evaluate the effect of vitamin C saturation on the course of this complication after it has once become established. This was done by maintaining vitamin C saturation in a test group of patients known to have tuberculous enteritis and by permitting a similar control group to continue unsaturated.

In the management of these cases, several additional features presented themselves and have proved of sufficient value to warrant a summary of the experience gleaned from this experience.

For purposes of the experiment both the test and control groups of patients were placed on a high calorie (approximately 3,200 calories daily), high carbohydrate diet, made up of bland, low residue foods. This was served in five portions. Very careful dietetic supervision was necessary to insure the ingestion of this amount of food, painstaking care being given to individual tastes and to the severity of intestinal symptoms. Diets were supplemented by the addition of Haliver Oil and Brewer's yeast. Food substances containing vitamin C were given in about the same amount as in the usual house diet at this institution. Considerable attention was given to the maintenance of adequate balance, particularly in patients exhibiting acute diarrhoea. For those patients suffering from severe anorexia or nausea and vomiting, the diets were modified to meet the individual needs. Small, frequent liquid feedings of gelatin or gruel mixtures were often used. At times it was necessary to rely on intravenous glucose to supply the necessary caloric intake.

Daily determinations were made of the six-hour urinary output of ascorbic acid. After finding a base line for each patient over a period of three days, a test dose of ascorbic acid (Hoffmann-LaRoche)[4] was administered to each patient in the test group in varying dosage until saturation was attained. From one to two grams were required in nearly all cases to achieve this result. Saturation was then maintained by continued administration of a daily dose determined by the urinary output. This amount varied from 50 to 300 mg. The

[1] From the Wm. H. Maybury Sanatorium (Detroit Municipal Tuberculosis Sanatorium), Northville, Michigan.

[2] Wm. H. Maybury Sanatorium (Detroit Municipal Tuberculosis Sanatorium), Northville, Michigan.

[3] Bellevue Hospital, New York, New York.

[4] Ascorbic acid for this study was generously supplied through the courtesy of Hoffmann-LaRoche, Inc.

control group of patients received a substitution of lactose but this was known only to the authors.

No effort was made to classify the pulmonary disease as to extent or character, but all cases were in the moderately or far advanced groups. Since it would be only confusing to attempt an evaluation of the part played by progression or retrogression of the pulmonary lesion, this aspect has been ignored and only alteration in abdominal symptoms considered.

Patients were selected clinically on the basis of such abdominal symptoms as diarrhoea, constipation or abdominal discomfort. Barium X-ray studies were then made according to the methods of Brown and Sampson (4) to confirm the diagnosis. In order to observe accurately any therapeutic improvement, it was necessary to eliminate all drugs which might obscure symptoms. Specifically eliminated were paregoric, bismuth and all laxative drugs other than small doses of mineral oil or milk of magnesia. Attention is called to this point in view of the surprising success encountered in controlling symptoms without recourse to medication.

RESULTS

Twenty-two patients were followed on this routine from October, 1938 until June, 1939, at which time the administration of ascorbic acid was terminated. The final observation was made on this group of patients in October, 1940. The resulting data follow in tabular form.

Name	Symptoms	Ascorbic acid	Result
J. M.	Constipation, anorexia, abdominal cramps, emesis	Yes	Symptoms controlled without recurrence. Death due to pulmonary disease.
A. H.	Anorexia, weight loss, vague abdominal pain	Yes	Symptoms controlled without recurrence. Living.
L. L.	Nausea, anorexia, intermittent constipation and diarrhoea, mild abdominal colic	Yes	Symptoms controlled. Recurred shortly before death due to pulmonary disease.
M. R.	Diarrhoea, severe abdominal cramps, anorexia	Yes	Symptoms uncontrolled. Death due to pulmonary and intestinal disease.
A. T.	Diarrhoea, abdominal tenderness, no cramps	No	Symptoms controlled with gain in weight and strength. Living.
M. G.	Anorexia and asthenia, nausea and vomiting	Yes	Nausea and vomiting controlled. Death due to respiratory insufficiency and toxaemia.
P. T.	Severe dyspnoea, moderate constipation, nausea and vomiting	Yes	Symptoms due to enteritis controlled. Death due to pulmonary disease.
M. M.	Diarrhoea, anorexia and severe abdominal cramps	Yes	Abdominal cramps relieved but diarrhoea and anorexia continued. Death due to respiratory insufficiency and toxaemia.
D. B.	Nausea, vomiting, anorexia and abdominal cramps	Yes	Symptoms controlled without recurrence. Death due to pulmonary disease.

Name	Symptoms	Ascorbic acid	Result
B. M.	Alternating diarrhoea and constipation, severe anorexia and vague abdominal pain	Yes	Symptoms controlled without recurrence, gain in weight and strength. Living.
L. S.	Nausea and vomiting, abdominal cramps and diarrhoea	Yes	Symptoms controlled without recurrence, marked gain in weight. Living.
B. P.	Right lower quadrant pain, anorexia and nausea	No	Symptoms controlled without recurrence, gain in weight and strength. Living.
F. B.	Vague abdominal pain, nausea and vomiting, diarrhoea	No	Nausea and diarrhoea subsided but some pain persisted. Ulcer perforated terminally.
I. S.	Occasional vague abdominal discomfort, anorexia	Yes	Symptoms controlled with terminal exacerbation. Death due to pulmonary disease.
P. M.	Extreme anorexia	Yes	Partially relieved. Living.
H. G.	Anorexia, abdominal cramps and severe diarrhoea	Yes	Symptoms controlled with terminal exacerbation. Death due to tuberculous meningitis.
T. W.	Occasional abdominal pain, intermittent constipation and diarrhoea, anorexia	Yes	Uncontrolled. Death due to intestinal and pulmonary disease.
E. R.	Abdominal cramps, diarrhoea and anorexia	No	Symptoms controlled without recurrence. Living.
E. J.	Abdominal discomfort, anorexia	No	Symptoms controlled without recurrence. Living.
G. L.	Abdominal cramps, nausea, diarrhoea and anorexia	No	Symptoms relieved except for some anorexia. Living.
E. V.	Abdominal pain and anorexia	No	Symptoms relieved without recurrence. Living.
L. M.	Severe abdominal cramps, diarrhoea and anorexia	No	Symptoms improved but not entirely relieved. Living.

In summarizing these results one finds that 14 patients were saturated with vitamin C for a period of nine months. In 6 of these there was excellent control of all symptoms, in 6 definite improvement, in 2 no response. Eight of the patients were maintained on a similar dietary regimen but without supplementary ascorbic acid. Five of these became symptom-free and 3 improved. The response, accordingly, was as satisfactory in the control group as in the experimental group. Combining the two groups, one finds that in a total of 22 patients studied, 20 were benefited to a varying degree, 11 of these being completely relieved of all symptoms.

There was no objective evidence that the course was altered in any way by saturation with vitamin C, but it is to be added that, in nearly every instance, patients voluntarily expressed a feeling of increased well-being at or near the point of saturation.

DISCUSSION

The result of dietary management of these cases proved so satisfactory that interest in this phase of the problem eventually overshadowed the problem of

vitamin C saturation. Since both the test and control groups responded equally well, it must be assumed that vitamin C saturation is not important in the therapy of intestinal tuberculosis after it is once established.

Kennedy and his coworkers (5) have recently shown excellent results in the dietary management of tuberculous enteritis. Aside from this report, however, scant importance has been attached to dietetic control of the distressing symptoms of this complication in spite of the common employment of some form of low residue diet. Unfortunately, routine low residue diets are usually unpalatable, monotonous and insufficiently flexible to meet the changing tastes and needs of the enteritis patient. It seems reasonable to approach this therapeutic problem with the point of view adopted in the management of comparable problems, such as typhoid fever or even peptic ulcer. In such cases we expect a good response to frequent small bland feedings, high in caloric value. It must be recalled that good results cannot be expected from dietary management unless the diet is eaten and that meticulous care is necessary to achieve this end. Daily rounds by a dietitian especially interested in the problem are of inestimable value. Whims of appetite must be humored constantly and the patient encouraged to coöperate as fully as possible. The degree of anorexia present makes it imperative that feedings be small, concentrated and appealing.

SUMMARY

1. Twenty-two patients with clinical and X-ray evidence of tuberculous enteritis were studied.

2. All were placed on a high calorie (approximately 3,200 calories daily), high carbohydrate diet made up of bland, low residue foods, served in five portions.

3. Fourteen patients were saturated with ascorbic acid for nine months and 8 were allowed to continue highly unsaturated.

4. Symptoms were well controlled in both groups by diet alone. No importance could be attached to ascorbic acid saturation in the control of symptoms of enteritis.

5. Many patients expressed a feeling of increased well-being at or near the point of saturation.

SUMARIO

1. Este estudio comprende 22 enfermos en que había datos clínicos y roentgenográficos de enteritis tuberculosa.

2. A todos se les impuso un régimen hiperhidrocarbonado y rico en calorías (unas 3,200 diarias), que estaba formado por alimentos blandos y de poco residuo, servidos en cinco porciones.

3. A los catorce enfermos se les saturó con ácido ascórbico por espacio de nueve meses, y a ocho se les dejó continuar sin la menor saturación.

4. En ambos grupos se cohibieron bastante bien los síntomas por medio de la alimentación exclusivamente, sin que se pueda conceder la menor importancia a la saturación con ácido ascórbico para cohibir los síntomas de la enteritis.

5. Muchos enfermos expresaron una sensación de hipereuforia al llegar al punto de saturación o acercarse a éste.

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CONTROL OF TUBERCULOSIS IN A LEPROSARIUM[1]

G. H. FAGET[2]

That tuberculosis is one of the most serious problems encountered in a leprosarium is attested by the mortality statistics of these institutions. Pineda (1) in a series of 300 consecutive autopsies at Culion found tuberculosis to be the most common cause of death. It was ascribed as the primary cause of death in 72 cases, an incidence of 24 per cent. Less extensive tuberculous lesions were present in 58 additional cases. Tuberculosis in one form or another then was a complication of leprosy in a total of 130 cases, or 43.3 per cent.

That this high incidence of tuberculosis is not solely a racial characteristic of the Filipino is shown in a later report by Lara *et al.* (2). These writers point out that in Manila in 1921 tuberculosis was the cause of 19.9 per cent of deaths while the Culion Colony rate was considerably higher, 32 per cent, for the same year. They considered the living conditions of the residents of the two localities (Manila and Culion) closely comparable. Moreover, the mortality statistics of other leprosaria show a similarly high incidence of tuberculosis. At the National Leprosarium at Carville, Louisiana during the last five years there were 161 deaths. Tuberculosis was considered to be the primary cause of death in 29, or 18 per cent. This high incidence of tuberculosis as the principal cause of death was confirmed in the 116 autopsies (72 per cent of the deaths) performed during the same period.

Since tuberculosis is such a commonly fatal complication of leprosy, the importance of its control in a leprosarium can easily be realized. It is probable that patients with leprosy are especially susceptible to exposure to tuberculosis. It is also probable that the predisposing factors of the two diseases may be the same, inadequate diet, poor personal hygiene, low economic status and overcrowded living conditions. At any rate, the frequency of tuberculosis among inmates of leprosaria has been noted throughout the world. Wayson (3), for example, reports that, in a group of 101 leprous patients whom he studied in Hawaii, 28 per cent proved to be tuberculous from the clinical and roentgenological findings as well as by animal inoculation and culture.

The primary step in the control of tuberculosis in a leprosarium is the early diagnosis of all cases of the disease and the segregation of those with open lesions. The diagnosis of pulmonary tuberculosis in a leprosarium is not so easy a task as in the general population. Many of the symptoms of the two diseases are similar. Fever, weakness and loss of weight are common complaints in both diseases. The hoarseness of leprous laryngitis may resemble that of tuberculous laryngitis. Fortunately the dysphagia which is such a troublesome symptom of advanced tuberculous laryngitis is seldom or never encountered in that due to leprosy. However, progressive mucosal leprosy frequently leads to laryngeal

[1] Published with the approval of the Surgeon General of the United States Public Health Service.

[2] Senior Surgeon, U. S. Public Health Service, National Leprosarium, Carville, Louisiana.

stenosis and suffocating attacks necessitating emergency tracheotomy, which is practically unknown in tuberculosis. The close similarity of the two diseases might be discussed further, but the parallelism in epidemiology, aetiology, symptomatology and treatment has already been the subject of numerous papers (4, 5) and need not be dealt with further here.

To emphasize the difficulty of tuberculosis diagnosis in a leprosarium, the unreliability of a positive sputum by the routine microscopic smear technique must be pointed out. It has been the experience at Carville (6), as in other leprosaria, that the Hansen bacillus is frequently expectorated in the sputum. These germs no doubt are exuded into the saliva and nasopharyngeal secretion from the buccal and nasopharyngeal mucosal lesions so common in lepromatous leprosy. Unless these acid-fast bacilli appear in the sputum in "globi" formation they cannot be distinguished from the tubercle bacilli. Their morphological and tinctoral characteristics are almost identical. In order to prove that acid-fast organisms found in the sputum are tubercle bacilli it is necessary to resort to animal inoculation or culture. This has been done in a number of cases at the National Leprosarium.

Whenever tuberculosis is suspected a careful physical examination of the chest should be done and certainly a roentgenogram of the lungs should be taken. This is the best way to arrive at a correct diagnosis. It has been found at the National Leprosarium that leprosy does not produce such gross pulmonary lesions as will cast visible shadows in the X-ray film of the chest. Leprosy of the lungs has been reported by Muir (7) and others but it is so rare as to be relatively unimportant. Most of the destructive lung lesions formerly attributed to leprosy have since been proved to be those of pulmonary tuberculosis. Jeanselme (8) states that pulmonary leprosy may exist as small white nodules or as a chronic peribronchial sclerosis. At the Carville Leprosarium gross pulmonary leprosy has not been recognized at postmortem examinations. The writer knows of no literature describing any X-ray findings attributable to leprosy of the lungs.

As a means of controlling tuberculosis in the National Leprosarium, routine roentgenograms of the lungs have been taken of all patients upon admission. Those showing X-ray evidence of pulmonary tuberculosis are kept in the infirmary for further observation and treatment. Since each patient has a separate room and minimal contact with fellow patients is allowed, new sources of infection are thereby limited. While the patient is in the hospital, examination of the sputum is instituted for the identification of the tubercle bacillus. Besides the routine entrance X-ray films, periodic roentgenological examinations are made on all inmates whenever deemed necessary. Since tuberculosis is prone to develop during the course of leprosy, expecially when the disease becomes advanced, the medical staff should be constantly on the alert for the development of this complication. All suspicious cases should be submitted to periodic X-ray examinations at six months' to a year's interval. Earlier diagnoses are made in this way and the patient is benefited by proper treatment. Incidentally the other patients are thereby protected. Serial X-ray films in our patients

afford comparative evidence of the onset and the progress of the pulmonary disease. Once the diagnosis of pulmonary tuberculosis has been made as a complication of leprosy, it should be treated along lines similar to those carried out in a modern sanatorium. Pulmonary tuberculosis seems to react equally favorably to treatment when leprosy is present as when it is not.

It cannot be too strongly stressed that tuberculosis is the disease to be treated primarily when it coexists with leprosy. It is generally found that the application of measures useful in the treatment of tuberculosis will also be beneficial to leprosy. On the contrary it is probably a mistake to continue the treatment of leprosy and disregard the existence of tuberculosis. The chaulmoogra oil treatment of leprosy is contraindicated in the presence of pulmonary tuberculosis. Lara and others (2) say, "There has been sufficient evidence to show that many of the patients with tuberculosis, who were given leprosy treatment died from this disease sooner then they would have died had they been left untreated. It was this conviction that led us later to suspend treatment in all tuberculous cases, with the result that the death rate for this disease in 1923 was lower than that for the previous year."

It is found that the routine triad of bed-rest, nutritious diet and fresh air works equally well in leprosy as in tuberculosis. Surgical collapse therapy should be used whenever feasible for pulmonary tuberculosis complicating leprosy. Artificial pneumothorax is the procedure of choice, since it is the simplest to institute and the element of time is of no importance. Phrenic exeresis, thoracoplasty and other serious chest operations are too severe for the leprosy patient. Since the patient will remain in the leprosarium for years, the more slowly and surely acting pneumothorax therapy is a more suitable form of pulmonary collapse.

The present study is based upon the observation of 400 patients for a period of six months to 2 and one-half years at the National Leprosarium. Among these patients a diagnosis of tuberculosis was made in 32, an incidence of 8 per cent.

During the period of observation 10 of these patients have died of tuberculosis. In 5 of them the diagnosis was made by routine X-ray examination on admission. The disease was already far advanced at the time and they lived only a few months following admission. In the other 5 the disease developed during the last stages of leprosy and progressed rapidly to death. There are 2 other far advanced cases which are doing fairly well on rest treatment, in which the diagnosis was made on admission. Seven active cases are now confined to the hospital on rest treatment.

Several patients with minimal or moderately advanced pulmonary tuberculosis have become quiescent or apparently arrested following rest treatment during the period of observation and have been returned to the ambulatory section of the colony. Since all patients at the leprosarium occupy separate rooms, close contact is limited and these patients are not considered a grave menace to others. The individual-room construction of the dormitories at the National Leprosarium has simplified the problem of management and control of tuberculosis

among the patients. It is felt that this has contributed in a large measure to the relatively low incidence of this disease among our patients.

Four patients with predominantly unilateral tuberculosis have recently been subjected to pneumothorax therapy. In one of them, a noncavity case, the compressed lung has been allowed to reëxpand and the patient is doing well at present with the disease apparently arrested. The other 3, all cavity cases, are doing satisfactorily under pneumothorax inflations. It is as yet too early to discontinue this treatment in any of them. Their prognosis, insofar as tuberculosis is concerned, seems favorable. Thus far no unfavorable acute leprous reactions have been encountered in connection with the air inflations. The writer was surprised that such reactions—*erythema nodosum* and *erythema multiforme*, so frequently seen in leprosy—were not produced by these pneumothoraces. Collapsing of a diseased lung by artificial pneumothorax is prone to cause the absorption of toxic products into the circulation. The presence of any toxic product in the blood stream in leprosy generally is sufficient to set up an acute leprous reaction. That these have not been observed in our small number of cases would suggest that pneumothorax collapse is a relatively harmless procedure in leprosy.

SUMMARY

1. Tuberculosis has been found to be one of the most common causes of death in leprosaria.

2. The similarity between leprosy and tuberculosis and other factors render the diagnosis of tuberculosis in a leprosarium more difficult than in the general population.

3. The control of tuberculosis in a leprosarium is one of the difficult problems with which the medical staff has to cope.

4. Early diagnosis and treatment with adequate isolation of open cases is the key to the problem.

5. When tuberculosis and leprosy exist conjointly, treatment should be aimed primarily against tuberculosis.

SUMARIO

1. La tuberculosis ha resultado ser una de las causas más comunes de muerte en los leprosarios.

2. La semejanza entre la lepra y la tuberculosis, así como otros factores, dificultan el diagnóstico de tuberculosis en un leprosario más que en la población general.

3. El dominio de la tuberculosis en un leprosario constituye uno de los problemas difíciles con que tiene que luchar el claustro médico.

4. La solución del problema estriba en el diagnóstico y el tratamiento tempranos, con aislamiento adecuado, de los casos abiertos.

5. Cuando coexisten tuberculosis y lepra, el tratamiento debe encaminarse primordialmente hacia la tuberculosis.

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THE PRACTICAL APPLICATION OF BRONCHOSPIROMETRY[1,2]

JOHN D. STEELE

Brochospirometry was first used to determine the functional capacity of each lung separately and simultaneously by Jacobaeus, Frenckner and Bjorkman in Sweden in 1932 (1). During his visit to America in 1937, shortly before his death, Jacobaeus demonstrated the value of the procedure to us in this country (2). Since that time, valuable contributions to the subject have been made by various American physicians (3, 4, 5, 6).

Since the functional capacity of a lung cannot be accurately predicted by roentgenological examination, the value of bronchospirometry has generally been conceded. However, the majority of thoracic physicians and surgeons seem to have the impression that the procedure is beyond the reach of those who do not have a research laboratory available. This impression has been gained because most of the literature on the subject, while of indispensable scientific value, has been fully comprehensible only to a small group of physicians who have made a particular study of respiratory physiology. It is the purpose of this article to emphasize that bronchospirometry is not necessarily a complicated procedure and, at least in a simplified form, can be performed in almost any hospital or sanatorium. The results so obtained are often of great value from a clinical standpoint.

Bronchospirometry is particularly valuable in a tuberculous patient who has a low respiratory reserve and for whom some irreversible collapse therapy procedure, such as thoracoplasty, is contemplated. In our experience, it has become an indispensable procedure in determining whether or not thoracoplasties should be performed on a certain small group of patients with low respiratory reserve. In another somewhat larger group, bronchospirometry, while not indispensable, has been of definite value and comfort in assuring us that functioning lung tissue will not be collapsed by a contemplated thoracoplasty.

In order to perform a bronchospirometry, it is necessary to insert a double-channeled instrument into the tracheobronchial tree so that the respiration of each lung can be measured separately and simultaneously. Inflatable balloons are used to keep the gaseous exchange of each lung separate and to prevent the entrance of air through the larynx from interfering with the determination. Jacobaeus, Frenckner and Bjorkman used a double-channeled bronchoscope for their bronchospirometries. In 1938, Gebauer (7) introduced a double-channeled soft rubber catheter which is less traumatizing and much more comfortable for the patient. In 1940, Zavod (8) described a similar catheter which seems to have a mechanical advantage over the original Gebauer catheter in that the balloons of the Zavod catheter can be inflated more easily and more accurately than those

[1] From the Departments of Surgery of Muirdale Sanatorium, Wauwatosa, Wisconsin, and of the Marquette University School of Medicine, Milwaukee, Wisconsin.

[2] Read before the meeting of the Mississippi Valley Trudeau Society, Chicago, September 18, 1942.

of the Gebauer catheter. Recently, however, we have replaced the balloons of the original Gebauer catheter with some of thinner rubber. With this alteration, there is little, if any, advantage in one catheter over the other.

After the double-channeled instrument is in place in the tracheobronchial tree, spirometers are connected to each channel in order to register the respiration of each lung. With special spirometers and with the use of gas analyses, oxygen consumption, carbon dioxide elimination, tidal air, supplementary and complementary air and vital capacity can all be determined. However, the equipment necessary for all of these determinations is not generally available and, furthermore, the use of such equipment requires the services of a trained technical staff. For clinical purposes, all of the above determinations are not essential. Bjorkman (9) was the first to point out that, in the evaluation of the functional capacity of a lung, the oxygen consumption is the most important and constant factor. Oxygen consumption alone can be determined easily and accurately with a standard basal metabolism apparatus. The use of metabolors for this purpose was originally advocated by Gebauer. Thus, if a separate basal metabolism apparatus is connected to each side of a bronchospirometry catheter, we can determine the most important function of each lung without the aid of a research laboratory. The oxygen consumption in litres per minute can easily be calculated from the resulting tracings and the relative function of each lung thus determined. It is not necessary that each metabolism apparatus be exactly similar in construction, since allowances can easily be made for differences in the size and shape of the oxygen containing cylinders. Since a patient is not under basal conditions during a bronchospirometry, the actual amount of oxygen consumed cannot be compared with "normal" values. The oxygen consumption of one lung is merely compared with the oxygen consumption of the other lung. Since carbon dioxide is absorbed by the soda lime in a basal metabolism apparatus, the vital capacity of the separate lungs cannot be determined.

A short description of the technique of bronchospirometry will be given in order to emphasize the simplicity and practicability of the procedure. The patient's pharynx and larynx are anaesthetized as for bronchoscopy. The patient is then placed on a horizontal fluoroscopic table. The larynx is exposed with a direct laryngoscope and a Zavod or Gebauer catheter is inserted into the trachea. One member of the team, whose eyes are accommodated, follows the course of the catheter fluoroscopically until the tip is located in the left main bronchus about three centimeters below the carina. The balloons are then inflated and each channel of the catheter is then connected to a basal metabolism apparatus by use of large rubber tubing and glass connection tubes. The drums of the metabolors are started and the determination begun. Since the catheter is flexible, a pillow may be placed under the patient's head to add to his comfort. If the catheter has been properly introduced, no anoxaemia or dyspnoea should develop as 100 per cent oxygen is being inspired from the cylinders of the metabolors. The determination may be run for eight minutes, which is the usual period required for a complete revolution of the cylinders.

In actual practice, every bronchospirometry does not run off as easily and as

simply as outlined above, but the great majority of them do after the operating team has had a little experience. The following difficulties and complications may be encountered. First, the larynx may be difficult or impossible to expose, in which case it may or may not be possible to pass the catheter indirectly through the larynx. Second, the patient's respiratory reserve may be so low that

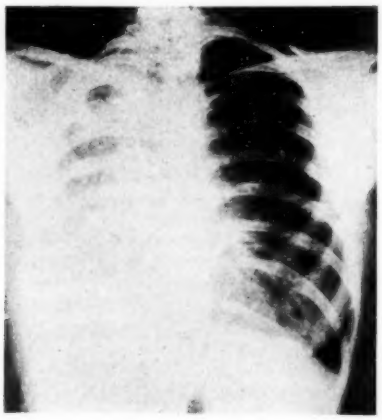

FIG. 1a. Chest roentgenogram (taken with the use of a Potter-Bucky diaphragm) of a twenty-nine year old woman who required a thoracoplasty for the control of the disease of her right lung. A 50 per cent collapse of the left lung by pneumothorax is present.

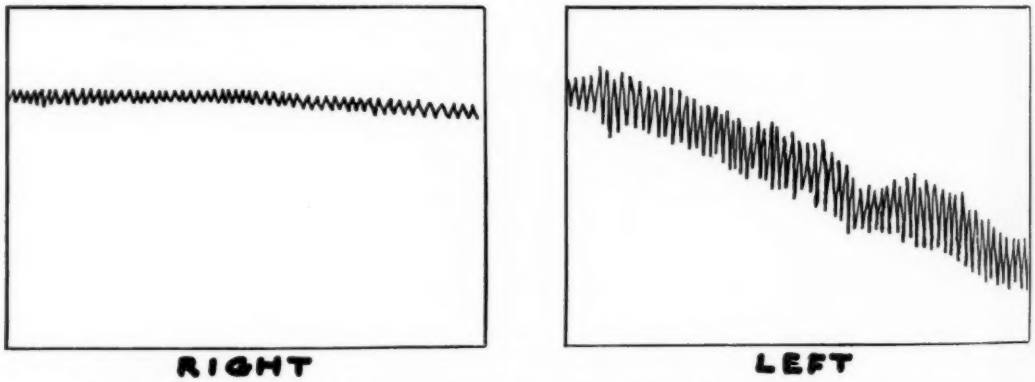

FIG. 1b. Bronchospirographic tracing of patient whose roentgenogram is shown in figure 1a. The right lung has consumed practically no oxygen.

the mere introduction of the catheter into the trachea may occasionally produce severe anoxaemia. In this case, it is wise to abandon the idea of a bronchospirometry. Such a patient is probably not a fit subject for collapse therapy anyway. Third, one or both channels of the catheter may become plugged with secretions, thus resulting in either a false determination or severe anoxaemia. In this case, it may be possible to repeat the procedure on another day following bronchoscopic aspiration of the secretions. Fourth, a stenosis of the left

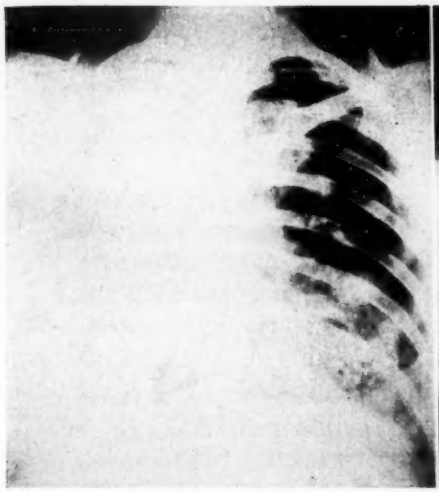

FIG. 2a

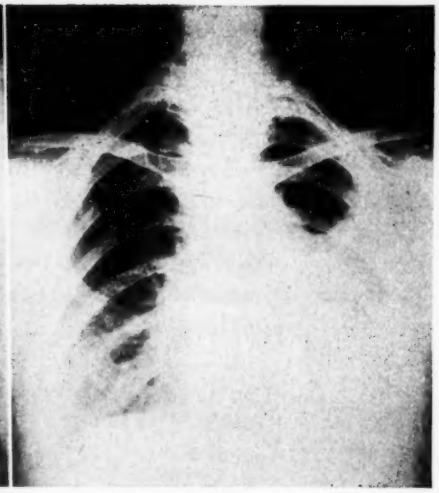

FIG. 3a

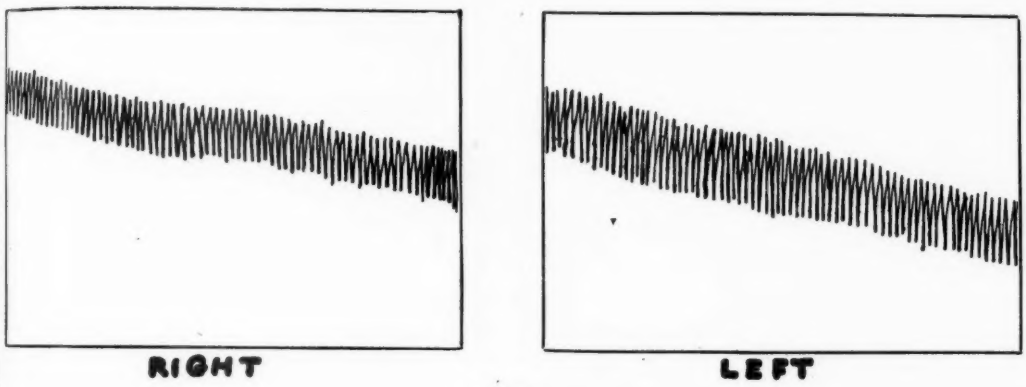

FIG. 2b

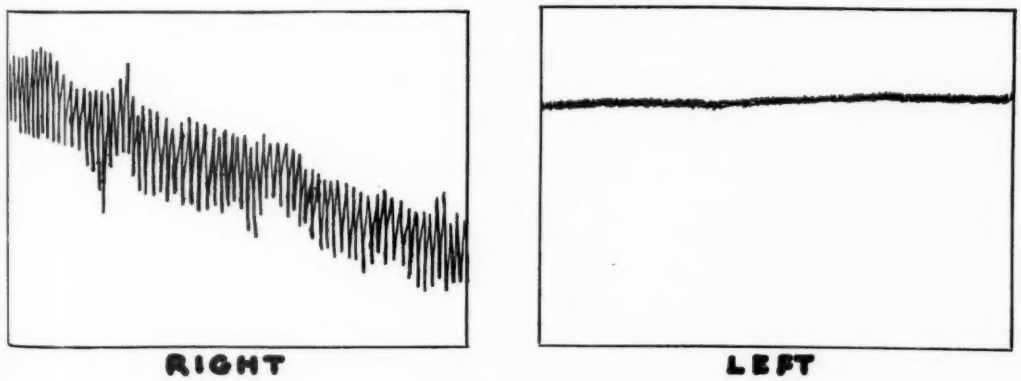

FIG. 3b

FIG. 2a. Chest roentgenogram of woman twenty-seven years of age. A 40 per cent collapse of the left lung by pneumothorax is present. Thoracoplasty was contemplated for control of the disease of the right lung.

FIG. 2b. Bronchospirographic tracing of patient whose roentgenogram is shown in figure 2a. Oxygen consumption is practically equal on both sides.

FIG. 3a. Chest roentgenogram of a forty-nine year old woman. A large tension cavity is present in the apex of the left lung.

FIG. 3b. Bronchospirographic tracing of patient whose roentgenogram is shown in figure 3a. The left lung has consumed no oxygen.

bronchus may prevent passage of the tip of the catheter into this bronchus. It is preferable that a bronchoscopy be done at some time prior to the bronchospirometry for this reason. Fifth, the connections may leak at some point causing a rapid fall of the metabolor cylinder, or air may leak in around the balloon in the trachea resulting in a rise of the metabolor cylinder instead of the expected fall. These difficulties are mentioned because we have encountered them. We feel sure that they must be encountered by all who perform bronchospirometries. As mentioned above, the majority of determinations run off smoothly. In particularly important cases, in which the decision as to collapse or not to collapse depends on the bronchospirometry, it is advisable to repeat the determination at least once.

The accompanying illustrations demonstrate the use of bronchospirometry in 3 patients each of whom is typical of the three groups of tuberculous patients previously mentioned. Figure 1a is a roentgenogram, taken with the use of a Potter-Bucky Diaphragm, of the chest of a twenty-nine year old woman who required a thoracoplasty for control of the disease of her right lung. A 50 per cent collapse of the left lung by pneumothorax was present. Her vital capacity was only 1,000 cc. Even though the roentgenogram showed some aeration of the right lung, bronchospirometry (figure 1b) revealed practically no oxygen consumption on this side. The left lung, partially collapsed by pneumothorax, was found to be carrying practically the entire respiratory load. Right thoracoplasty has been completed without incident. Thoracoplasty would probably not have been performed if the findings on bronchospirometry had not been so favorable.

The patient, a female twenty-seven years of age, whose roentgenological and bronchospirographic findings are illustrated in figures 2a and 2b, presented a similar indication for right thoracoplasty. Her vital capacity was 900 cc. A 40 per cent collapse of the left lung by pneumothorax was present. Even though there was less apparent aeration of the right lung on the roentgenogram than in the case of the first patient, bronchospirometry revealed practically equal oxygen consumption on both sides. Thoracoplasty was, therefore, not performed.

The third patient, a woman forty-nine years of age, had a large tension cavity at the left apex (figure 3a). Cavity drainage followed by thoracoplasty appeared to be indicated. She was not a good thoracoplasty risk. Her vital capacity was 1,000 cc. It was, therefore, reassuring to know that the left lung was functionless (figure 3b) before starting the collapse therapy. Monaldi cavity drainage was performed following a preliminary anterior thoracoplasty. An eight-rib posterior thoracoplasty was subsequently completed without incident.

SUMMARY

The value of bronchospirometry in the evaluation of patients with pulmonary disease has been generally conceded, but the procedure has not come into widespread use because it is too often believed that bronchospirometry cannot be performed without the aid of a research laboratory. Actually, valuable clinical results can be obtained in any hospital or sanatorium by determining the oxygen consumption of each lung separately by connecting an ordinary basal metabolism

apparatus to each side of a double-channel soft rubber catheter which has been introduced into the tracheobronchial tree.

SUMARIO

En general se ha aceptado el valor de la broncoespirometría para justipreciar los casos de enfermedad pulmonar, pero el procedimiento no se ha generalizado debido a creerse injustificadamente que no puede ejecutarse la broncoespirometría si no se cuenta con un laboratorio de investigación. En realidad pueden obtenerse valiosos resultados clínicos en cualquier hospital o sanatorio, determinando por separado el consumo de oxígeno de cada pulmón, conectando un aparato corriente de metabolismo basal a cada lado de una sonda de goma blanda de dos vías que se ha introducido en el árbol tráqueobronquial.

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AN EARLY PRIMARY TUBERCULOUS PULMONARY FOCUS[1]

About Four to Eight Weeks Old

WALTER PAGEL AND DOROTHY STOPFORD PRICE

There are still only three instances on record of an early primary tuberculous lung focus (Zarfl 1913 (5), Ghon and Roman 1915 (2), Ghon and Pototschnig 1919 (1)). Our scanty knowledge of the changes in human beings has been supplemented by experimental observations in animals (Pagel 1925, 1926 (3, 4)). A further instance, probably the earliest described so far, is therefore of particular interest.

This is a female infant whose mother and elder sister suffer from advanced pulmonary tuberculosis. The child was born at home, on July 31, 1942. From the fifth week on, the infant was watched for the development of primary tuberculosis. A skiagram of the chest and Mantoux test (1:100) on September 9, 1942 were negative. Four Moro tests and three further chest skiagrams, taken at weekly intervals, were negative, but a further Mantoux test (1:100) was positive on October 4. At this time the child was suffering from gastro-enteritis: there was vomiting, diarrhoea and pyrexia to 100° F. for five days. The infant died three days later when she was sixty-eight days old. No tuberculous changes were discovered either at necropsy or when the lungs were sectioned after formalin fixation. An area 2 x 2 mm. in size in the right lower lobe, looking inadequately fixed, and five other areas from various parts of the lungs were examined in serial sections. In addition, the lymph node at the bifurcation, two groups of bronchopulmonary and two paratracheal glands (one from each side) were sectioned.

In none of these lymph nodes were tubercle bacilli or tuberculous changes discovered, nor were there any changes in the five areas of lung tissue examined at random.

The part which appeared inadequately fixed contained a focus, 0.9 x 1.2 mm. in size (figure 1). It was neither encapsulated nor sharply demarcated from the surrounding lung tissue and the septa of its elastic alveoli were filled with lymphocytes. This lymphocytic infiltration was obviously an extension from the small focus which showed interstitial accumulation of lymphocytes and, in addition, mononuclear and plasma cells throughout. These interstitial accumulations caused a chess-board-like appearance by separating a number of ectatic alveoli from each other. The elastic framework of the alveolar septa was well preserved. The alveoli were filled with material which was cellular at the periphery and consisted of partly homogeneous plugs in the centre of the focus. In the peripheral alveoli, the cells were typical "alveolar epithelial cells" (alveolar phagocytes) and, in addition, there were similar mononuclear elements of the reticular cell type (figure 2). In the homogeneous alveolar plugs of the central areas (figure 3) the cells were recognizable in shadowy outlines only and their

[1] From the Pathology Department, Central Middlesex County Hospital, London, N.W. 10, and St. Ultan's Hospital, Dublin.

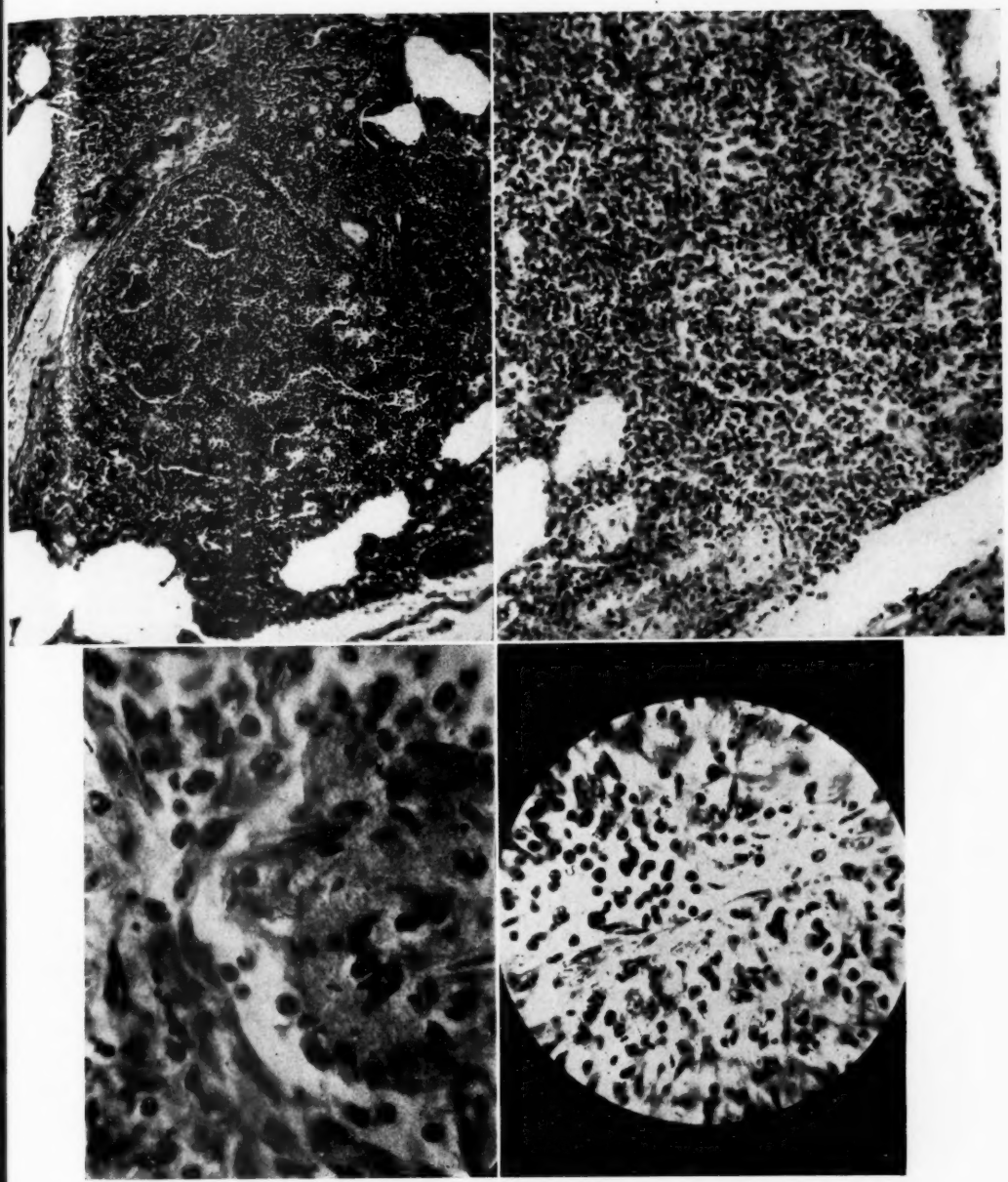

FIG. 1 (upper left). Survey showing the whole focus. Alveolitis with beginning patchy caseation. The focus occupies an acinus, the terminal bronchiolus of which enters on top right. Intense interstitial infiltration with lymphocytes.

FIG. 2 (upper right). Close-up of alveolitis before caseation. Alveoli filled with "alveolar phagocytes." Intense lymphocytic infiltration of alveolar septa.

FIG. 3 (lower left). Close-up of alveolitis with beginning caseation. Numerous tubercle bacilli. Ziehl-Neelsen.

FIG. 4 (lower right). Close-up of interstitial infiltration. Numerous tubercle bacilli. Ziehl-Neelsen.

nuclei showed various degrees of necrobiosis. A large number of typical acid-fast bacilli were discovered both in the homogeneous alveolar plugs and in the infiltrated septa (figure 4).

The whole focus (figure 1) occupied a lung acinus attached to a small bronchiolus which entered sideways at one of its corners.

The main features of the focus may briefly be summarized as follows:

1: An alveolitis, in which desquamation of "alveolar epithelial cells" and accumulation of macrophages are the most conspicuous changes.
2: Caseation, patchy and limited to some small cellular plugs inside the alveoli in the centre of the focus; it does not alter the elastic alveolar framework.
3: An intense interstitial reaction, the whole of which occupies a bigger portion of the focus than the patchy alveolitis.
4: Alveolar plugs as well as interstitial parts containing numerous acid-fast rods.
5: No trace of a fibrous capsule or of tubercles.

The histological details suggest, therefore, that this was a very early focus. The picture seems to be identical with that described by Zarfl (1913). The nodules observed by Ghon and Roman (1915) and Ghon and Pototschnig (1919) were probably older.

In the cases just quoted only remnants of the alveolar septa were preserved and caseation seemed to be more wide-spread than in our case. In both instances the hilar lymph nodes were involved and contained epithelioid-celled tubercles. In Zarfl's case no histological examination of the lymph nodes was made. Our observation affords definite proof that the lung focus antedates changes in the hilar lymph nodes. These have been sectioned and found devoid of changes.

It is difficult to assess the actual age of the focus. Allowing for a preallergic "incubation" period of three to seven weeks, it may be assumed that it developed within four to eight weeks before death.

It may be deduced from the early changes seen in our case that multiplication of the bacillus in the alveoli is followed by a process restricted to them (alveolitis). Desquamated "alveolar epithelial cells" (alveolar phagocytes) and mononuclear cells then accumulate. The cellular plugs in the alveoli are subject to necrosis and the nuclei show all stages of pycnosis, caryorrhexis and caryolysis while the protoplasmatic bodies become confluent and form a homogeneous ground substance. While these changes take place, bacilli penetrate into the alveolar septa in which large numbers of lymphocytes and mononuclear cells collect. This interstitial reaction is particularly intense in the neighborhood of the caseous alveoli. In the periphery of the focus there is a tendency for the lymphocytes to be arranged in circles.

This is the stage of development reached in the focus of our case. It may be assumed that the next stage would be an extension of caseation to the interstitial tissue. The focus would then assume the picture of a homogeneous area of caseous bronchopneumonia with remnants of elastic fibres; in the peripheral area of lymphocytic demarcation, connective tissue would form a capsule. This is

the familiar picture of a primary focus. It shows neither alveolar plugs with beginning caseation nor intense reaction of alveolar septa to the penetration of bacilli into the interstitial tissue. These features, typical of an early focus, have been described in the experimental animal (Pagel 1925, 1926).

SUMMARY AND CONCLUSION

1. A primary lung focus about four to eight weeks old is described in an infant aged two months; the hilar lymph nodes were not affected.

2. The changes were (*a*) patchy alveolitis of the desquamative, macrophagocytic type, (*b*) caseation restricted to the alveolar plugs in the centre of the focus.

3. A strong lymphocytic and mononuclear cell infiltration of the septa with acid-fast rods was observed.

SUMARIO Y CONCLUSIÓN

1. Descríbese un foco pulmonar primario de unas 4 a 8 semanas de duración en una criatura de dos meses; no se afectaron los ganglios linfáticos del hilio.

2. Las alteraciones consistieron en: (*a*) alveolitis en placas del tipo macrofagocitario descamado; (*b*) caseación limitada de los taponcillos alveolares del centro del foco.

3. Se observó una intensa infiltración linfocitaria y mononuclear con bastoncillos ácido-resistentes.

The authors' thanks are due to Mr. J. E. Mayhew and Mr. H. Pegler for technical assistance.

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PROMIN IN EXPERIMENTAL TUBERCULOSIS IN THE GUINEA PIG[1, 2]

E. M. MEDLAR AND K. T. SASANO

The chronicity of tuberculosis, its stubborn resistance to therapy and a tendency to relapse are features that are indelibly engraved upon the mind of all who have been intimately associated with the care of tuberculous patients. That no entirely satisfactory therapeutic procedure for the treatment of tuberculosis has been devised is clearly indicated by the volume of literature which deals with a large variety of clinical and surgical methods of treatment. Chemotherapy has received considerable attention but has not attained any large degree of success.

A new wave of hope and endeavor in the field of tuberculous infection has accompanied the spectacular clinical results that have been reported from the use of the Sulfonamide group of chemicals in a considerable variety of acute bacterial infections. The first reports which deal with the effects of chemicals of the Sulfonamide group on artificially induced tuberculous infection in experimental animals appeared in 1938. A good summary of the earlier investigations is included in an article by Ballon *et al.* (1). In the majority of instances the results of these experiments were equivocal with slightly favorable to negative conclusions. The more recent reports added no note of great encouragement, until Feldman *et al.* (2) reported that promin exerted a spectacular effect upon the retardation of tuberculous infection in the guinea pig.

Two valid criticisms may be made of all the experiments that have been reported. First, all of the experiments have been of a relatively short duration when one bears in mind the chronic nature of tuberculous infection in man. Second, no report, in which favorable results have been obtained, has given a *complete* experiment in which results subsequent to discontinuance of drug therapy have been detailed. In a chronic infection such as tuberculosis the results subsequent to therapy are of as great importance as are the immediate effects of a course of treatment. The main purpose of this report is to put on record a *complete* experiment on the effect of promin upon experimentally induced tuberculous infection in the guinea pig.

In an experiment of this type there are certain factors that must receive due consideration in the "set-up" of the experiment. First, a considerable number of animals must be used, for it is well known that there is quite a variation in individual "resistance" within a group of experimental animals. Second, the dosage of tubercle bacilli must be sufficiently small so that a relatively chronic disease will be established, for that is the situation encountered in human tuberculous infection. Third, the infection must be allowed to gain a "foothold" before therapy is begun for no human tuberculous infection is ever detected before a definite disease process is well established. In guinea pigs a lapse of one to

[1] From the Hegeman Research Laboratory, Metropolitan Life Insurance Company Sanatorium, Mount McGregor, New York.

[2] The promin used in this experiment was supplied by Parke, Davis & Company, to whom we are indeed grateful for their generous assistance.

two weeks is necessary to allow the bacilli to be spread throughout the body, from a subcutaneous inoculation, if culture of the organisms from macerated spleen may be used as a criterion as to how soon the dissemination of bacilli occurs. And, fourth, the acid-test of any chemotherapy is to determine the course of events after the treatment is concluded. All of these factors have been given due consideration in the experiment here reported.

The guinea pigs used in the experiment were of the multicolor type and averaged about 350 g. in weight. Both male and female were included in the group and the sexes were maintained separately. One hundred animals were given a subcutaneous injection of 0.02 mg. (moist weight) of a two-week old culture of tubercle bacilli (H37) in the groin. The H37 strain of human tubercle bacillus is known to vary at times in its pathogenicity and at the time of the experiment our culture was known to possess a moderate degree of virulence. Ten days after the inoculation the animals were divided into two equal groups with one as a control

TABLE 1

Comparative data on control and promin treated animals

Promin therapy was discontinued at five months after infection. Deaths shown in column one occurred during period when promin was being administered

GROUP	CAUSE OF DEATH	CUMULATIVE DEATHS IN FIVE-MONTH PERIODS					TOTAL	AVERAGE SURVIVAL
		5	10	15	20	23		
								days
Control	Tuberculosis	30	46	48	—	—	48	146
	Nontuberculous	2	—	—	—	—	2	124
Promin	Tuberculosis	—	2	5	9	11	11	413
	Nontuberculous	4	16	28	35	39*	39	364

* One animal was sacrificed to end the experiment.

and the other for chemotherapy. The treated animals were fed, by pipette, 300 mg. of promin daily for five months at which time all therapy was stopped and the experiment continued until all of the animals died. The experiment was begun in mid-January, 1941 and all animals but one were dead by mid-December, 1942, a lapse of twenty-three months. The sole surviving animal was in good condition when sacrificed and showed only a localized tuberculous abscess at the site of inoculation. The results of the experiment are given in table 1.

The data as given in table 1 do not mean that no evidence of tuberculosis was present in the animals listed under nontuberculous deaths. The 2 animals so listed in the control group showed a progressing tuberculous infection but death was due to acute lobar pneumonia. Of the 39 animals recorded as nontuberculous deaths in the promin group, 26 showed no macroscopical evidence of tuberculous infection, except for small shotty lymph nodes in the groin on the side of inoculation and 13 showed small firm tuberculous foci in the lungs, liver or spleen. All of the deaths recorded as tuberculous showed the macroscopical findings so

commonly observed in guinea pigs dying from uncomplicated tuberculous infection. The findings in the promin group differed in some respects from the control in that there tended to be more fibrosis and encapsulation of lesions, that is, a somewhat more chronic type of progressive infection.

Cultures were made from digested splenic tissue in 22 of the animals that failed to show macroscopical evidence of tuberculous infection in the viscera. The 4 animals that died during the course of therapy were not cultured. In 17 instances cultures were obtained with the number of colonies varying from one to many. Failure to obtain growth of bacilli in 5 instances does not necessarily indicate that no tubercle bacilli were present. It is apparent that these animals have not been able to eradicate completely the tuberculous infection, although they have succeeded in developing sufficient immunity to hold the infection in abeyance for a considerable period. These findings emphasize how difficult it is to eradicate completely the tubercle bacillus once it has gained entrance to tissue.

Mention may be made of another experiment now in progress in which the daily dose of promin has been reduced to 100 mg. and in which chemotherapy was not begun until three weeks after the date of the inoculation of tubercle bacilli. To date there have been no deaths due to tuberculosis in the promin group, although the last of the control animals has been dead for three months.

DISCUSSION

There are two main reasons for the report of this experiment. First, there is conclusive evidence that promin exerts a definite inhibitory effect upon the progression of experimentally induced tuberculous infection in the guinea pig. Second, we have been unable to find the recording of an experiment which gives information relative to the course of events after promin therapy is discontinued. This consideration is of prime importance where therapy in human tuberculous infection is under discussion, for it is well known that in man tuberculosis tends to be a relapsing disease even with the best of therapy.

It is very evident that tuberculous infection was not eradicated by promin under the conditions of our experiment. While only 22 per cent of the treated animals died from uncomplicated tuberculous infection subsequent to the discontinuance of therapy, tubercle bacilli were demonstrated in the viscera in 80 per cent. It is quite possible that a higher percentage of positive results might have been obtained had a more extensive culture of the viscera for tubercle bacilli been made. The question that remains unanswered is whether the bacilli demonstrated in the "no-visible-lesion" viscera would have been the source from which a lethal tuberculous infection might have eventually developed. On the other hand promin therapy accomplished results that we have not been able to obtain in any other way in experimental tuberculosis and many chemical compounds have been given trial during the past twenty years. The encouraging results obtained warrant further studies in chemotherapy to discover a compound or compounds that will do even better than promin. One thing, of course, must be borne in mind—a chemical that may act favorably in the guinea pig may not accomplish the same results in man.

In the experiment here reported we believe that the dosage of promin was unnecessarily large. Evidence is now at hand that one-third of the amount first employed exerts a very favorable effect. It is planned to determine how small a dosage will affect the course of the disease.

In our experiment the factors of "natural resistance" to infection had a chance to become apparent. In the control group the first tuberculous death occurred in sixty-three days and the last in three hundred twenty-seven days. After discontinuance of promin therapy the first animal to succumb to the "delayed" tuberculous infection died in ninety-three days and the last in four hundred fourteen days. We regard these animals as those of the promin group that had little if any "natural resistance" and once the chemotherapy was stopped the infection progressed in much the same way as if no therapy had been given—that is, these animals were unable to develop a significant immunity to the disease. Other animals with the aid of chemotherapy developed such a high degree of immunity to the tuberculous infection that no macroscopical evidence of disease in the viscera was present a year or more after the therapy was discontinued.

If it be true that the results subsequent to promin therapy depend so much upon the presence or absence of the factors of "natural resistance" then considerable light is thrown upon the rôle of the Sulfonamide compounds in chemotherapy. That none of these compounds are bacteriocides in concentrations allowable in any therapy is well known. That most of the compounds exert a bacteriostatic effect *in vitro* is also well known. However, *in vitro* bacteriostatic effects do not necessarily indicate that the same results may be attained *in vivo*. In experiments now in progress we have found that sulfathiazole is bacteriostatic *in vitro* in considerably higher dilutions than is promin. On the other hand, tuberculous guinea pigs fed equal amounts of the two chemicals show a very different picture. None of the promin treated group has died from tuberculosis three months after the last of the sulfathiazole treated animals had succumbed to the disease. Since the bactericidal and the *in vitro* bacteriostatic properties of these chemicals do not seem to be the crucial factors in Sulfonamide chemotherapy, the unknown and seemingly undeterminable factors of "natural resistance" would seem to assume increased significance. It may well be that these chemical compounds exert a very important "delaying action" not connected with either bactericidal or bacteriostatic properties and in this way the tissues are enabled to muster completely all available factors of "natural resistance." If, during therapy, these forces become sufficiently potent, a high degree of resistance or immunity may be maintained against the infection once the therapy is discontinued; if not, the infection progresses when therapy is stopped. Sulfonamide chemotherapy is still in the experimental stage. The tendency has been to use as high a dosage of the chemicals as the tissues can tolerate on the assumption that bactericidal or bacteriostatic effects may be attained. Due consideration has not been given to the part played by the tissues themselves. With chemicals as toxic to tissues as is this group of compounds greater effort should be made to determine how little of the drug is necessary to give nature a chance to assert herself. It is possible that these chemicals should be used in a supportive rather than in a dominant rôle.

Whenever chemotherapy in clinical tuberculosis is considered certain aspects of tuberculous infection as a whole must be borne in mind. The large majority of persons who become infected with the bacillus never develop a clinical disease and probably represent that part of the infected population that has a good "natural resistance" to the infection. These persons are able to develop a high degree of resistance or immunity. The smaller group, the ones who occupy the beds of institutions for the tuberculous, are mostly the ones with relatively little "natural resistance." Under medical care, which acts as a splint to a broken bone, many of the patients with moderately or far advanced disease are improved and under a somewhat sheltered existence may live with their disease for a long time. To expect any spectacular and immediate effect from chemotherapy in tuberculosis, as seen in tuberculous institutions, is to disregard the soil in which the infection is present. To demand results similar to those obtained in acute lobar pneumonia is to forget that about the only thing in common between the two diseases is that they occur in the same organ. Recently Zucker *et al.* (3) reported that promin therapy does not alter the expected course of tuberculosis. These authors administered from 100 to over 1,000 g. of promin during a period ranging from two to eight weeks and based their conclusions on clinical observations up to six months after discontinuance of therapy. From our experience with experimental tuberculosis we do not believe that the data presented by these authors prove that promin may not exert a beneficial effect on the course of pulmonary tuberculosis. One point has been clarified—massive doses of promin will not prevent the progression of the disease in some cases. It is quite possible that a smaller amount of chemical administered over a much longer period of time might produce favorable results in individuals who do not have a too extensive disease. One should not expect the tissue damage present in tuberculous foci to be repaired very quickly under any circumstance. The results to be expected by any chemotherapy in tuberculosis must be tempered by the knowledge that the disease is chronic in nature, that the repair of tissue damage is slow and that the majority of tuberculous patients in sanatoria have only a limited ability to resist the infection. The extermination of the infecting agent by promin therapy should not be anticipated.

SUMMARY AND CONCLUSIONS

Promin therapy, begun ten days after virulent tubercle bacilli were injected subcutaneously in the groin of guinea pigs, was administered for a period of five months at which time the treatment was discontinued and the experiment was extended until all the treated animals died. The last survivor was sacrificed eighteen months after the therapy was stopped. Ninety-two per cent of the animals in the promin group were alive when therapy was discontinued. Of these animals, 24 per cent died of uncomplicated generalized tuberculosis, 28 per cent exhibited small localized tuberculous foci in spleen, liver or lung, and 48 per cent showed no macroscopical evidence of visceral tuberculosis. Cultures of tubercle bacilli were obtained from the spleen in 77 per cent of the animals that showed no

macroscopical evidence of visceral tuberculosis. Positive cultures were obtained as long as seventeen months after the discontinuance of therapy.

Promin therapy retarded the tuberculous infection very decidedly but did not eradicate the infection in our experiment. Similar results have not been observed in numerous other chemotherapeutic tests made during the past twenty years. Such favorable results warrant further chemotherapeutic studies to reveal chemical compounds that may be even better than promin.

The probable rôle of the factors of natural resistance is discussed and the necessity of greater recognition of these factors in human tuberculosis, whenever any chemotherapeutic studies are undertaken, emphasized.

In studies of this type care should be exercised to avoid overoptimism prior to a very thorough investigation of the subject if for no other reason than the psychological reaction of those ill with the disease. The history of "cures" for tuberculosis should make one very cautious in making any overstatement of fact. It is extremely difficult to determine when any individual infected with the tubercle bacillus has completely eradicated the disease.

SUMARIO Y CONCLUSIONES

Durante un período de seis meses se administró la prominoterapia, iniciada a los diez días de inyectarse bacilos tuberculosos virulentos subcutáneamente en la ingle de un grupo de cobayos, después de lo cual se suspendió el tratamiento y se continuó el experimento hasta que murieron todos los animales tratados. El último sobreviviente fué sacrificado dieciocho meses después de suspenderse la terapéutica. Al suspenderse ésta, noventa y dos por ciento de los animales del grupo tratado con prominoterapia estaban vivos. De esos animales, 24 por ciento murieron de tuberculosis generalizada (granulia) simple, 28 por ciento manifestaron pequeños focos tuberculosos localizados en el bazo, hígado o pulmón, y 48 por ciento no revelaron signos macroscópicos de tuberculosis visceral. Obtuviéronse bacilos tuberculosos del bazo en 77 por ciento de los animales que no revelaron signos macroscópicos de tuberculosis visceral. Continuaron obteniéndose cultivos positivos hasta diecisiete meses después de suspenderse la terapéutica.

La prominoterapia retardó muy decididamente la infección tuberculosa, pero no la erradicó en este experimento. No se han observado resultados semejantes en otros numerosos ensayos quimioterapéuticos ejecutados durante los últimos veinte años. Esos resultados favorables justifican la ejecución de nuevos estudios quimioterapéuticos, a fin de descubrir compuestos químicos que pueden resultar hasta mejores que la promina.

Discútese el probable papel de los factores de la resistencia natural y la necesidad de conceder mayor reconocimiento a esos factores en la tuberculosis humana, siempre que se emprendan estudios quimioterapéuticos.

En los estudios de este género debe tenerse cuidado a fin de evitar el hiperoptimismo antes de hacer una investigación muy completa del asunto aunque no aunque no fuera más que por la reacción psicológica de los enfermos. La historia de "curas" de la tuberculosis debe infundirnos la mayor cautela

para evitar exageraciones, siendo sumamente difícil determinar cuándo un individuo infectado por el bacilo tuberculoso ha erradicado completamente la dolencia.

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DEMONSTRATION OF TUBERCLE BACILLI IN MINIMAL PULMONARY TUBERCULOSIS[1]

W. P. DECKER, W. H. ORDWAY AND E. M. MEDLAR

The importance given to the detection of pulmonary tuberculosis in the minimal stage of the disease is well known to all who are cognizant of the broad aims of the general tuberculosis program. It is also well understood that in the diagnosis of such cases fluoroscopic and roentgen-ray film examinations are a necessity, since very few patients exhibit any clinical manifestation of the disease in the early stages. Since the diagnosis rests almost wholly upon the observation of shadows in certain locations in the lung field, the demonstration of tubercle bacilli in the minimal cases is required to clinch the clinical diagnosis. This report presents the results obtained in this institution with the intensive use of the more thorough laboratory methods in the study of clinically active cases of minimal pulmonary tuberculosis. Such activity had as its essential requirement an unstable pulmonary lesion, as demonstrated by serial roentgen-ray films taken over a reasonable period of time.

There is little in the literature which deals directly with this problem. Stiehm (1) reported the demonstration of tubercle bacilli in 15 out of 21 cases of minimal disease. Barton (2) reports the finding of tubercle bacilli in 44 cases of minimal pulmonary tuberculosis as follows: by direct smear, 2; by smear of concentrate, 1; by culture, 8; and negative by all methods, 33. A recent report (3) from this institution indicated that tubercle bacilli were demonstrated in 27 out of 59 cases. Oyama (4) reported the demonstration of tubercle bacilli in 35 of 79 cases of primary infection and in one of the positive cases the X-ray film of the chest was normal; in 19 of 47 cases of pleural effusion; in 30 of 42 cases of early infiltration; and in 11 of 19 cases of apical tuberculosis. It is difficult to determine just how many of these cases would be classed as clinically active minimal pulmonary tuberculosis according to the National Tuberculosis Association standards. Kruger *et al.* (5) believe that it is unnecessary to try to demonstrate tubercle bacilli in the early cases prior to the institution of treatment, as the diagnosis is practically always obvious from the clinical and roentgenological examination of the patient.

The routine use of gastric lavage and of culture and guinea pig inoculation of concentrated specimens on all minimal cases was begun in this institution in 1936. Prior to that date only the patients who had expectoration were examined repeatedly by sputum concentrates and guinea pig inoculations if smears were negative. To compare the results of the laboratory studies two periods were selected: 1930–1935 and 1936–1941. It is generally recognized that persons in the early minimal stage often do not raise sputum. The proportion of "sputum" and "no sputum" cases for the two periods chosen are given in table 1.

It is to be noted that the ratio between "sputum" and "no sputum" cases is

[1] From the Metropolitan Life Insurance Company Sanatorium, Mount McGregor, New York.

practically the same for these two periods. In the first period only the "sputum" cases were studied for tubercle bacilli, while in the second period all the cases were adequately investigated by the more searching laboratory methods. The results of these studies for the two periods are given in table 2.

The marked increase of positive results shown in the second period demonstrates clearly the value of repeated examinations by culture and animal inoculation. This is further emphasized by the results obtained in the period 1939–1941, when even more through investigations were made, for during that period 92.9 per cent of the "sputum" and 80 per cent of the "no sputum" cases were proved to be positive. Throughout the study an especial effort was made to obtain an initial seventy-two-hour sputum or three consecutive facting gastric contents as soon as the patient was admitted. One-half of the cases in which tubercle bacilli were obtained were proved from this initial series of tests. If these initial tests were negative it was often necessary to make many tests

TABLE 1

Distribution of "sputum" and "no sputum" cases

PERIOD	NUMBER OF CASES	"SPUTUM"	"NO SPUTUM"
1930–1935	172	71 (41.3%)	101 (58.7%)
1936–1941	97	41 (42.2%)	56 (57.8%)

TABLE 2

Positive results obtained on "sputum" and "no sputum" cases of minimal pulmonary tuberculosis

PERIOD	NUMBER OF CASES	"SPUTUM"		"NO SPUTUM"	
		Number of cases	Per cent positive	Number of cases	Per cent positive
1930–1935	172	71	33.8	101	–
1936–1941	97	41	63.4	56	73.2

before bacilli were demonstrated. One example of this is a case in which bacilli were not demonstrated until the fifteenth series of gastric contents were examined.

Patients admitted to this institution come from all portions of the United States and Canada east of the Rocky Mountains. They may be classed into "Home Office" and "Field" regions. At the Home Office in New York City all employees have for years had yearly examinations which included fluoroscopy and, if deemed advisable, roentgen-ray films of the chest. Such has not been the general procedure in the Field. It is of interest then to compare the distribution of cases relative to the Home Office and the Field. These data are given in table 3.

In table 3 it will be noted that during the first period the ratio of "sputum" to "no sputum" cases was practically reversed in the two groups. During this period the "no sputum" cases were not investigated for the presence of tubercle

bacilli and in the "sputum" cases approximately the same percentage of positive results were obtained in the two groups. While the reverse ratio in "sputum" and "no sputum" cases in the two groups is not as great in the second period, it is still present. The change noted here may be due to the more general use of fluoroscopy and of roentgen-ray films in the detection of the early tuberculous case. It will also be noted that a considerably higher percentage of positive results was obtained in both groups due to the greater effort made to demonstrate tubercle bacilli. The reason for a higher percentage of positive results in the Home Office than in the Field group is not clear unless it can be ascribed to the earlier discovery of the lesion in a "fresh" exudative stage when bacilli may be more readily demonstrated.

A point of interest not shown in table 3 is the percentage of cases in which sputum smears were positive. For the period 1930–1941 29 per cent of the Home Office and 64 per cent of the Field group raised sputum. Positive smears were found in about the same percentage in the two groups, 12 per cent for the Home Office and 16 per cent for the Field. When the "no sputum" cases were

TABLE 3

Distribution of cases on basis of "sputum" and "no sputum" with percentage of positive results obtained in "home office" and "field" groups

PERIOD	GROUP	TOTAL CASES	"SPUTUM"		"NO SPUTUM"	
			Number of cases and per cent	Per cent positive	Number of cases and per cent	Per cent positive
1930–1935	Home Office	111	29 (26)	34.5	82 (74)	—
	Field	61	42 (70)	33.3	19 (30)	—
1936–1941	Home Office	61	21 (35)	76.2	40 (65)	80
	Field	36	20 (55)	50.0	16 (45)	56.2

included in each group, the Home Office group gave 3.5 per cent of positive smear cases while the Field gave 10.3 per cent of positive cases. Taking the groups as a whole, positive smears were found in 5.9 per cent of the cases. This is in marked contrast to the 69 per cent positive results obtained on all cases when a more thorough laboratory study was done during the period from 1936 to 1941.

DISCUSSION

These studies have clearly demonstrated to us that there is a great variation, in cases of minimal pulmonary tuberculosis, in the number and frequency of discharge of tubercle bacilli. An occasional patient will discharge bacilli in such numbers that practically all smears of sputum examined will be positive, whereas another individual with a similar clinical and roentgenological picture will be found to discharge few bacilli on a rare occasion or not at all. From the pathogenesis of a tuberculous lesion one may postulate that, since the primary parenchymal tuberculous focus is but a small "open" area of bronchopneumonia,

all lesions of this type may discharge bacilli. It is not necessary to have demonstrable "cavity" formation prior to the discharge of bacilli from a tuberculous focus any more than it is necessary to have "cavity" formation before bacteria may be discharged from an early area of bronchopneumonia caused by streptococci or pneumococci. Kruger *et al.* (5) state: "At the same time we wish to stress the fact that a more recent analysis made by us of the frequency of bacillary sputum in noncavernous tuberculosis, even after adequate search, fails to confirm the high incidence of positive results reported by some observers." The acceptance of this statement depends entirely upon the interpretation of the words "sputum" and "adequate search." We believe that a high percentage of minimal tuberculous patients discharge a small amount of exudate from their bronchi but that in the majority of these cases the amount is so small that they are not conscious of "raising" anything from the lungs. This is the reason why it is necessary to obtain fasting gastric washings for study. If by "adequate search" is meant the examination of smears of "sputum" in the usually accepted sense, then it is agreed that only a small percentage of cases of minimal pulmonary tuberculosis will be found positive. In our group of 269 cases, in only 16 (5.9 per cent) was it possible to demonstrate tubercle bacilli in a smear of sputum. By the repeated use of cultures and guinea pig inoculations from concentrates of smear-negative sputum or of gastric washings we have increased the positive results from 5.9 to 69 per cent.

The following case clearly illustrates this discussion. Serial roentgenograms of the chest showed an unstable lesion. The patient discharged a small amount of purulent sputum daily. Numerous smears, both direct and of the sputum concentrate, failed to demonstrate tubercle bacilli. The individual was not clinically ill. Every culture of the sputum concentrate gave a fairly abundant growth of tubercle bacilli and every guinea pig inoculated developed tuberculosis. The private physician of this patient maintained that if it was so difficult to demonstrate tubercle bacilli such findings were of little consequence and it took many months of tactful persuasion before the patient was finally hospitalized. It required about a year of residence in the hospital before the sputum became intermittently negative by culture and guinea pig tests.

Since the use of repeated tests by culture and guinea pig inoculation on sputum and on gastric washings have been instituted, a high degree of corroboration of the clinical diagnosis of minimal pulmonary tuberculosis has been obtained. During the period 1939–1941 34 cases were studied and pathogenic tubercle bacilli were demonstrated in 29. There are two possible explanations for the failure to demonstrate the bacilli in 5 cases. First, the laboratory examinations may not have been made at the right time or in sufficient numbers. Second, there is a possibility that the lesion in these negative cases was not caused by the tubercle bacillus, for it is well known that other infections do occur in the pulmonary fields where tuberculous lesions are prone to develop. One may categorically state that the modern clinical diagnosis of minimal pulmonary tuberculosis has a very high percentage of accuracy. To regard the diagnosis as infallible is hardly the right attitude to assume. Perfection is rarely achieved in any branch of medicine.

Kruger *et al.* (5) advise the examination of repeated gastric contents and of sputum to determine whether, at the end of the course of treatment, tubercle bacilli are present. Stiehm (1) regards negative results after repeated tests as indicative of healing of the lesion. From the experience we have gained from our studies we wish to caution against placing too great emphasis upon a series of negative tests. In the first place, unless the presence and frequency of discharge of tubercle bacilli are determined at the time of discovery of the lesion or in the very early phases of treatment, then no yardstick is available to gauge the significance of a series of negative tests. Second, a series of such negative tests does not necessarily indicate a healed lesion. Two cases come to mind that illustrate these points. Two or three positive results were obtained shortly after these 2 patients entered the hospital and no further positive results were obtained from monthly tests during a period of two years. In one case the last specimen obtained proved to be positive after the patient was discharged and in the other case a positive result was obtained after the patient has returned to work. To date there has been no X-ray or clinical evidence of a relapse of the disease in these 2 cases. At the present time it is very difficult to determine when a minimal case of pulmonary tuberculosis ceases to discharge a few bacilli and to evaluate the significance of an occasional discharge of a few bacilli.

SUMMARY

Repeated examinations of sputum and of fasting gastric contents by culture and guinea pig inoculation have resulted in the demonstration of tubercle bacilli in 67 out of 97 patients with clinically active minimal pulmonary tuberculosis over a period of five years. In a previous five-year period, when the more thorough laboratory methods were not in routine use, tubercle bacilli were demonstrated in only 24 of 172 cases.

Gastric lavage studies gave positive results in 41 of 56 "no sputum" cases.

Sputum smears were positive in but 16 of 269 cases. This is no true indication of the number of patients who were discharging tubercle bacilli.

A very high percentage of clinically active minimal tuberculous patients discharge tubercle bacilli to a greater or lesser degree.

It is very difficult to determine when patients with minimal disease are entirely free from bacilli. It is just as difficult to evaluate the significance of the discharge of a few bacilli on rare occasions.

SUMARIO

Los exámenes repetidos del esputo y del contenido gástrico en ayunas, por medio del cultivo y de la inoculación al cobayo, han permitido descubrir bacilos tuberculosos en 67 de 97 enfermos que habían tenido tuberculosis pulmonar mínima y clínicamente activa, durante un período de cinco años. En un quinquenio previo, en que no se empleaban sistemáticamente las técnicas de laboratorio más perfectas, sólo se encontraron bacilos tuberculosos en 24 de 172 casos.

Los lavados gástricos resultaron positivos en 41 de 56 casos "sin esputo."

Los frotes del esputo sólo resultaron positivos en 16 de 269 casos, pero esto

no constituye una indicación exacta del número de enfermos que expulsaban bacilos tuberculosos.

Un porcentaje muy elevado de los tuberculosos mínimos clínicamente activos, expulsaban en mayor o menor grado bacilos tuberculosos.

Es dificilísimo determinar cuándo los tuberculosos mínimos quedan absolutamente desembarazados de bacilos, y es igualmente difícil justipreciar la importancia de la expulsión de algunos pocos bacilos en raras ocasiones.

We desire to express our appreciation of the technical assistance rendered by Miss Edith Titworth and Miss Dorothy Caldwell.

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A MASS METHOD FOR CONCENTRATING AND STAINING TUBERCLE BACILLI[1]

FREDERICK W. La CAVA and MARY E. KETCHUM

The object of this paper is to present some refinements in concentrating and and staining tubercle bacilli so that sputum and other fluids can be examined in large numbers in a short period of time with an increase in the concentration of the organisms and in the staining qualities.

In examining sputum and other fluids for tubercle bacilli, the actual content of the organisms either by weight or volume is relatively small indeed. In a plain smear the organisms are so dispersed that it necessitates examination of a large area, and it is time consuming. The rationale of concentration lies in the use of certain chemicals which will dissolve everything but the tubercle bacilli so that they will then occupy a small space on a microscope slide. This theoretical possibility is not yet a practicality and our concentration methods are still relatively crude. The common methods in use at the present time are: sodium hydroxide in 4 per cent aqueous solution, as described by Petroff (1), trypsin as used by Haynes (2), and a combination of tergitol, sodium hydroxide and water as described by Petroff and Schain (3).

The method we propose is a modification of the tergitol mixture which we believe produces a better concentration of the tubercle bacilli. Tergitols are sodium secondary alcohols containing 10 to 21 carbon atoms near the centre of the hydrocarbon chain. Tergitol penetrant 08 is a sodium octyl sulphate and produces a marked reduction in surface tension, which factor is apparently the key to a more complete concentration.

In the usual heat method of staining the organisms, the high temperature required causes annoying precipitation of stain on the slide and is time consuming, especially when each slide must be handled individually. In the method we propose, the stain need not be filtered; mass staining can be done; the temperature used is 40°C.; and the resulting smears from the concentrate are so small in bulk that 2 or 3 specimens can be put on a single slide.

CONCENTRATION OF SPUTUM

The sputum is collected in wide-mouthed one-ounce bottles, sealed with a rubber stopper, and the specimen fills the bottle about one-third. These bottles are previously autoclaved, washed in hot soapy water, rinsed well, soaked overnight in potassium dichromate cleaning solution, and again rinsed in water. The rubber stoppers are boiled in a weak solution of tincture of green soap and rinsed in water. When the bottles are received in the laboratory they are identified by numbers and treated as follows:

1: Fill the bottle with the "digestion mixture" containing one part tergitol 08 and three parts 4 per cent sodium hydroxide.

[1] From the Hopemont Sanitarium, Hopemont, West Virginia.

2: Place in a shaking machine and shake for twenty minutes. In the absence of a shaking machine, keep them at room temperature for one hour and shake by hand at fifteen-minute intervals. (It may be noted at this point that thick heavy specimens may resist complete digestion by this or any other methods.)
3: Pour the resultant fluid into 35 cc. titre tubes which have previously been numbered.
4: Centrifuge at about 2,000 r.p.m. for ten minutes, thus resulting in a fluid and a sediment.
5: Pour off the supernatant fluid and invert the tubes on paper towels.
6: Scrape the sediment from the bottom of the tube and make small, fairly dense, circular smears on numbered slides. Due to the fact that the sediment obtained is small in volume, three small evenly spaced smears may be placed on a slide. These are identified by scratching the specimen number directly under each smear.

The above method can be used also on pus from abscess, pleural and gastric fluids and on precipitated sediments of urine and spinal fluids. The sediment obtained can also be used for cultures for tubercle bacilli.

COMPARISON WITH OTHER METHODS

Table 1 shows in detail the various attributes of three common concentration or digestion mixtures as compared to the one proposed. In the sodium hydroxide

TABLE 1

Results of quantitative comparisons of four techniques based upon 100 sputum specimens from 10 patients

DIGESTION MIXTURE	SPECIFIC GRAVITY	SURFACE TENSION	VISCOSITY	DIGESTION TIME	SEDIMENT	NUMBER OF BACTERIA PER FIELD
			seconds	*minutes*		
4 per cent sodium hydroxide	1.036	95.0	3.5			
Trypsin	1.050	20.0	3.5			
Tergitol (Petroff and Schain)	1.050	5.0	4.5			
Tergitol (La Cava and Ketchum)	1.050	3.0	3.5			
RESULTANT FLUID AFTER DIGESTION BY THE METHOD OF:						
4 per cent sodium hydroxide	1.051	33.2	4.0	31	2+	14
Trypsin	1.055	43.4	57.5	72	4+	3
Tergitol (Petroff and Schain)	1.051	9.4	56.5	85	3+	15
Tergitol (La Cava and Ketchum)	1.051	3.7	3.4	7	1+	21
Water (as standard)	1.000	100.0	3.0			

The surface tension was measured with a DeNouy surface tension machine. For the determination of viscosity a calibrated burette was used which was standardized to allow 10 cc. of water to fall in three seconds.

method the sputum is mixed with 4 per cent sodium hydroxide and placed in an incubator. After digestion is completed, the specimen is centrifuged, supernatant fluid is poured off and the sediment is neutralized and washed with water. The specimen must be recentrifuged before it can be smeared or inoculated. This method produces a fluid of low viscosity, a small sediment and a good degree of concentration. It increases the surface tension, making it difficult to

centrifuge the mixture and to separate the organisms from the more fluid portion. It takes an average of thirty-one minutes to digest the sputum.

The Haynes trypsin method uses a specially prepared mixture of a Seitz-filtered trypsin solution which is mixed with the sputum. Our experience with this method has been disappointing. Not only does it take a long time for digestion but it also leaves a large sediment, a poorer concentration and a high degree of culture contamination with other organisms.

Petroff and Schain use a digestant mixture of one part tergitol, one part water and one part 4 per cent sodium hydroxide. This produces a lowering of the surface tension of the fluid to be examined, but in all other features seems to be inferior to the use of straight 4 per cent sodium hydroxide. Our method using one part tergitol and three parts 4 per cent sodium hydroxide and no water produces a low surface tension, short digestion time, small sediment and a high concentration. Why this latter method should give better results we do not know, but since tergitol acts solely as a depressant of surface tension, allowing a better digestion of the fluid by the sodium hydroxide, then perhaps the addition of water in the method of Petroff and Schain dilutes the sodium hydroxide and weakens its action. We have, on the other hand, omitted the water and have tripled the amount of sodium hydroxide. In a control series of 100 sputa examined using tergitol-sodium hydroxide solution, we found 7 per cent more positives than with the 4 per cent sodium hydroxide method.

METHOD OF STAINING

We use a modification of the glycerin-fuchsin stain of Czaplewsky in these parts: 16 g. basic fuchsin, 300 cc. of 10 per cent phenol and 500 cc. of glycerin.

Place the basic fuchsin in a mortar and add slowly a 10 per cent phenol solution which has previously been heated to 70°C. Grind and mix well. Add this mixture to the glycerin which has also been heated to 70°C. Shake well and store over night. Place the stain in a deep dish and set in a water bath at 40°C. when in use. This stain will keep six months and will not need filtering at any time. With this stain the tubercle bacilli will be large, solid and thick in appearance. This may be due to the low temperature and the glycerin. The excess stain is easily removed from the slide with water.

The decolorizer consists of 97 cc. of 95 per cent alcohol and 3 cc. of hydrochloric acid. A 2 per cent aqueous solution of brilliant green is used for the counterstain.

Technique for Staining

1: Air-dry the slides and fix with heat.

2: Place the slides in a regular tissue staining rack which holds from 10 to 50 slides, each slide having one to three smears.

3: Immerse the entire rack of slides in the stain for ten minutes at 40°C.

4: Wash the slides thoroughly in water and decolorize in acid-alcohol until the smears are a faint pink. (One-half to one minute)

5: Wash thoroughly in water and place in the counterstain for two minutes.

6: Wash again and then dry the rack and slides either in the open air or in front of an electric fan.

SUMMARY

1. A combined method of concentrating and staining is presented whereby a team of two people can prepare 200 specimens for microscopic examination in four hours.

2. The tergitol-sodium hydroxide mixture proposed produces a high concentration in a short period of time.

3. The modified stain and technique proposed can be used at 40°C. for only ten minutes with a resultant excellent staining quality of the tubercle bacilli.

4. The resultant sediment is so small that 3 or even 4 specimens can be safely smeared on each standard microscope slide.

SUMARIO

1. Descríbese una técnica combinada para concentración y coloración que permite a un grupo de dos personas preparar en cuatro horas 200 ejemplares para examen microscópico.

2. La propuesta mezcla de hidrato de sodio y tergitol produce una concentración elevada en un período de tiempo breve.

3. La coloración y técnica modificadas propuestas pueden emplearse a 40°C. por sólo diez minutos, dando por resultado una excelente coloración de los bacilos tuberculosos.

4. El sedimento resultante es tan pequeño, que pueden hacerse sin temor 3 ó 4 frotes en cada portaobjetos corriente.

We gratefully acknowledge the invaluable assistance of Dr. David Salkin, Hopemont Sanitarium, and Dr. Eugene DeAngelis of the West Virginia University School of Medicine, Morgantown, West Virginia.

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MULTIPLE BACTERIOLOGICAL AETIOLOGY IN CLINICAL TUBERCULOSIS[1]

Experimental Observations

HILDRUS A. POINDEXTER

Observations on the laboratory correlation of the number and type of "secondary" microörganisms in sputum obtained from cases of pulmonary tuberculosis with the clinical course of the disease in these patients on comparable regimen prompted us to execute the protocol given below and present the results.

Sixty guinea pigs of 300 to 420 g. in weight were divided into five groups of 12 each. Table 1 contains the observations on 12 guinea pigs inoculated subcutaneously with 0.5 cc. of pure cultures of *Mycobacterium tuberculosis* isolated from the sputum of clinical cases of pulmonary tuberculosis in the Freedmen's Hospital Annex and with standard H37 strains in the instances marked by asterisks. The number of microörganisms was the same in each of the 12 guinea pigs, namely, 500,000 in 0.5 cc. The site of the injection was the right groin. The first series is presented as a control and standard for our stock guinea pigs.

The first and second columns are self explanatory. The third column represents the number of days which elapsed between the injection of the organism and the death of the animal. The fourth column is designed to show the percentage and type of "secondary" organisms that were found in important organs or tissues along with tubercle bacilli at autopsy. The autopsies were performed as early after death as practicable to avoid the postmortem invasion of the normal flora of the intestinal and respiratory tracts. When "secondary" microorganisms were present they were generally coliform or pyogenic cocci.

In the experiments presented in table 2, one of the commonly found "secondary" organisms of the sputum was mixed with an equal number of *Mycobacterium tuberculosis*, namely, 250,000 of the latter and 250,000 *Monilia candida* in a suspension of 0.5 cc. The inoculation was made in this series of guinea pigs in the same manner as in the first series. The table contains the observations. *Monilia candida*, Hansen and Berkhout, in pure culture is normally nonpathogenic for man or guinea pigs. *Monilia candida*, even though normally nonpathogenic for guinea pigs, at autopsy was found in the spleen along with tubercle bacilli in 75 per cent of this series. In 2 instances, guinea pigs No. 3 and 8, there were suppurative lesions between the layers of the abdominal muscles and some serofibrinous peritonitis in which *Monilia candida* was isolated alone with the *Mycobacterium tuberculosis* and staphylococci. All of these animals gave positive tuberculin reactions after sixteen days of infection, and some gave slight cutaneous reactions to extracts of *Monilia candida* also. The reactions were negative in noninfected animals.

Table 3 shows the effects of *Streptococcus mitior vel viridans* of Schottmüller on the clinical course of experimental tuberculosis in guinea pigs. This or-

[1] From the Department of Bacteriology, Preventive Medicine and Public Health of Howard University and Freedmen's Hospital, Washington, D. C.

TABLE 1

Guinea pigs inoculated with pure cultures of Mycobacterium tuberculosis

GUINEA PIG NUMBER	ULCERATION AT SITE OF INOCULATION	DEATH	PRESENCE OF "SECONDARY" ORGANISMS IN S, L, LN AND O† AT AUTOPSY	PRESENCE OF MYCOBACTERIUM TUBERCULOSIS IN S, L, LN AND O AT AUTOPSY
		days		
1	−	51	S..... +‡ L..... 0 LN..... 0 O..... 0	S..... + L..... + LN..... + O..... +
2	−	59	S..... +‡ L..... 0 LN..... 0 O..... 0	S..... + L..... + LN..... + O..... +
3*	−	54	S..... +‡ L..... 0 LN..... 0 O..... 0	S..... + L..... + LN..... + O..... +
4*	−	51	S..... 0 L..... 0 LN..... 0 O..... 0	S..... + L..... + LN..... + O..... +
5	−	50	S..... + L..... + LN..... 0 O..... 0	S..... + L..... + LN..... + O..... +
6*	−	60	S..... 0 L..... 0 LN..... 0 O..... 0	S..... + L..... + LN..... + O..... +
7	−	47	S..... 0 L..... 0 LN..... 0 O..... 0	S..... + L..... + LN..... + O..... +
8	−	70	S..... 0 L..... 0 LN..... 0 O..... 0	S..... + L..... + LN..... + O..... +
9*	−	56	S..... 0 L..... 0 LN..... 0 O..... 0	S..... + L..... + LN..... + O..... +
10	+	32	S..... 0 L..... 0 LN..... 0 O..... 0	S..... + L..... + LN..... + O..... +

TABLE 1—(*Continued*)

GUINEA PIG NUMBER	ULCERATION AT SITE OF INOCULATION	DEATH	PRESENCE OF "SECONDARY" ORGANISMS IN S,‡L, LN AND O† AT AUTOPSY	PRESENCE OF MOCOBACTERIUM TUBERCULOSIS IN S, L, LN AND O AT AUTOPSY
		days		
11	−	53	S..... 0 L..... 0 LN..... 0 O..... 0	S..... + L..... + LN..... + O..... +
12*	−	53	S..... 0 L..... + LN..... 0 O..... 0	S..... + L..... + LN..... + O..... +

* Inoculated with standard H37 strains.

† S = Spleen; L = Liver; LN = Regional lymph nodes; O = Other tissues, especially bones, joints and brain.

‡ + = Organisms are present; − = Organisms are not present.

ganism is not uncommonly found in the spleen or in such foci as sinuses, root canals of teeth or crypts of tonsils in persons with clinical pulmonary tuberculosis.

In addition to the special organs and tissues where *Streptococcus viridans* was found at autopsy, as shown in column 4 of table 3, we would like to emphasize that it was also found in the blood stream in 50 per cent of the animals either before death or at autopsy. *Streptococcus viridans* was found in the endothelially lined cavities of 33.3 per cent of the animals, and in this group the joint cavities were the most commonly involved. The postmortem cultures from the spleen and liver of animals in this series showed enterococci and coliform organisms in several instances.

The tuberculin tests were positive on all animals of this series after the sixteenth day of the infection. The animals also appeared to be allergic to *Streptococcus viridans* or its extracts. A group of 3 additional guinea pigs was infected in the same manner as the other 12 of this series, and after sixteen days was skin-tested with tuberculin and extracts of *Streptococcus viridans*. The reactions were positive to both, but the tuberculin tests were more pronounced. When 0.5 cc. of a phosphate buffer solution containing 0.025 mg. of tuberculin purified protein derivative (Mulford PPD) was injected into these sensitized guinea pigs, Koch's phenomena developed and the accelerated clinical courses resulted in early fatalities. When 0.5 cc. of a forty-eight hour broth culture of *Streptococcus viridans* or the extracts from that organism were injected into these sensitized guinea pigs, the reactions were almost similar to those observed in guinea pigs injected with 0.5 cc. of the standard second dose of tuberculin. The clinical courses were accelerated and the average death occurred within seven days after the injection of *Streptococcus viridans* extracts.

Mycobacterium tuberculosis was found in practically all of the tissues of the guinea pigs. Animals injected with the living cultures of *Streptococcus viridans*

TABLE 2

Guinea pigs inoculated with Mycobacterium tuberculosis and Monilia candida—Hansen and Berkhout

GUINEA PIG NUMBER	ULCERATION AT SITE OF INOCULATION	DEATH	PRESENCE OF "SECONDARY" ORGANISMS IN S, L, LN AND O AT AUTOPSY	PRESENCE OF MYCOBACTERIUM TUBERCULOSIS IN S, L, LN AND O AT AUTOPSY
		days		
1	−	56	S..... + L..... 0 LN..... 0 O..... 0	S..... + L..... + LN..... + O..... +
2	−	50	S..... + L..... 0 LN..... 0 O..... 0	S..... + L..... + LN..... + O..... +
3*	+	40	S..... + L..... 0 LN..... 0 O..... +	S..... + L..... + LN..... + O..... +
4	−	51	S..... + L..... 0 LN..... 0 O..... 0	S..... + L..... + LN..... + O..... +
5	−	56	S..... 0 L..... 0 LN..... 0 O..... 0	S..... + L..... + LN..... + O..... +
6*	−	52	S..... 0 L..... 0 LN..... 0 O..... 0	S..... + L..... + LN..... + O..... +
7	+	52	S..... 0 L..... 0 LN..... 0 O..... 0	S..... + L..... + LN..... + O..... +
8	+	45	S..... + L..... 0 LN..... 0 O..... +	S..... + L..... + LN..... + O..... +
9*	−	50	S..... + L..... 0 LN..... 0 O..... 0	S..... + L..... + LN..... + O..... +

TABLE 2—(*Continued*)

GUINEA PIG NUMBER	ULCERATION AT SITE OF INOCULATION	DEATH	PRESENCE OF "SECONDARY" ORGANISMS IN S, L, LN AND O AT AUTOPSY	PRESENCE OF MYCOBACTERIUM TUBERCULOSIS IN S, L, LN AND O AT AUTOPSY
		days		
10	–	49	S..... +	S..... +
			L..... 0	L..... +
			LN..... 0	LN..... +
			O..... 0	O..... +
11	–	41	S..... +	S..... +
			L..... 0	L..... +
			LN..... 0	LN..... +
			O..... 0	O..... +
12*	–	47	S..... +	S..... +
			L..... 0	L..... +
			LN..... 0	LN..... +
			O..... 0	O..... +

showed these organisms well distributed along with *Mycobacterium tuberculosis*, but those injected with the bacteria-free extracts of *Streptococcus viridans* only showed the *Mycobacterium tuberculosis* in several organs with an occasional post-mortem coliform invasion.

Table 4 is presented to show some of the effects of *Staphylococcus aureus* on the clinical course of experimental tuberculosis in guinea pigs. *Staphylococcus aureus*, either haemolytic or nonhaemolytic, was one of the most frequent non-acid-fast microörganisms found in sputum from clinical cases of pulmonary tuberculosis. It might well be considered a part of the normal flora of the mouth with pathogenic potentialities.

The strong pyogenic response of the body to *Staphylococcus aureus* infection and the necrotizing power of the toxin elaborated by this staphylococcus were reflected in the high percentage of ulcerations at the site of the inoculation. The microscopical sections showed soft, poorly developed tubercles in which the microörganisms were widely diffused in the tissues. The local and focal responses were predominantly polymorphonuclear, while in the animals injected with tubercle bacilli without the *Staphylococcus aureus* or other pyogenic organisms, the responses were primarily mononuclear.

Guinea pigs inoculated subcutaneously with 0.5 cc. of a twenty-four hour broth culture of *Staphylococcus aureus* alone showed ulcerations at the site of the inoculation which generally healed within forty-five days. If this infection were permitted to proceed without treatment, it would not kill the animal within one hundred and twenty days. If, however, some of these animals infected with *Staphylococcus aureus* without *Mycobacterium tuberculosis* are sacrificed after thirty to sixty days of the infection, pyaemic areas may be found in several organs of the body, including the kidney, spleen, liver and bones. Blood cultures

TABLE 3

Guinea pigs inoculated with Mycobacterium tuberculosis and alpha-haemolytic Streptococcus viridans of Schottmüller

GUINEA PIG NUMBER	ULCERATION AT SITE OF INOCULATION	DEATH	PRESENCE OF "SECONDARY" ORGANISMS IN S, L, LN AND O AT AUTOPSY	PRESENCE OF MYCOBACTERIUM TUBERCULOSIS IN S, L, LN AND O AT AUTOPSY
		days		
1	+	22	S..... +	S..... +
			L..... +	L..... +
			LN..... 0	LN..... +
			O..... 0	O..... +
2	−	36	S..... +	S..... +
			L..... 0	L..... +
			LN..... 0	LN..... +
			O..... 0	O..... +
3*	+	25	S..... +	S..... +
			L..... 0	L..... +
			LN..... +	LN..... +
			O..... +	O..... +
4	−	30	S..... 0	S..... +
			L..... 0	L..... +
			LN..... 0	LN..... +
			O..... 0	O..... +
5	−	30	S..... 0	S..... +
			L..... +	L..... +
			LN..... 0	LN..... +
			O..... 0	O..... +
6*	−	40	S..... 0	S..... +
			L..... 0	L..... +
			LN..... 0	LN..... +
			O..... 0	O..... +
7	+	19	S..... +	S..... +
			L..... +	L..... 0
			LN..... +	LN..... +
			O..... +	O..... 0
8	+	27	S..... +	S..... +
			L..... +	L..... +
			LN..... 0	LN..... +
			O..... 0	O..... +
9*	+	25	S..... +	S..... +
			L..... +	L..... +
			LN..... 0	LN..... +
			O..... 0	O..... +

TABLE 3—(*Continued*)

GUINEA PIG NUMBER	ULCERATION AT SITE OF INOCULATION	DEATH	PRESENCE OF "SECONDARY" ORGANISMS IN S, L, LN AND O AT AUTOPSY	PRESENCE OF MYCOBACTERIUM TUBERCULOSIS IN S, L, LN AND O AT AUTOPSY
		days		
10	–	50	S..... 0 L..... 0 LN..... 0 O..... 0	S..... + L..... + LN..... + O..... +
11	–	29	S..... + L..... + LN..... 0 O..... 0	S..... + L..... + LN..... + O..... +
12*	–	31	S..... + L..... + LN..... 0 O..... 0	S..... + L..... + LN..... + O..... +

were often positive. Pregnancy and the subsequent delivery in infected animals often cause wide extension of the organisms and earlier fatalities to the mothers. When pregnant guinea pigs infected with *Mycobacterium tuberculosis* and *Staphylococcus aureus* delivered, the foetus were often dead or died within the first two days after birth.

Table 5 presents the chief observations on results obtained from an experiment designed to show the effects of several viable organisms on the clinical course of experimental tuberculosis in guinea pigs. The material injected was undigested sputum, freshly collected from an active case of pulmonary tuberculosis, showing a Gaffky count of 5. The containers used for the collection were clean and free from disinfectants.

The detrimental effects of these "secondary" microörganisms on the clinical course of the disease in guinea pigs seemed to be more than those of mere symbiosis. Their multiple action seemed to be one of real synergism with mutual potentiation between some of them. The saprophytic spirochetes, or one of their facultative anaerobic complements, survived in the deep tissues of the abscesses and ulcers for at least fourteen days, as revealed by microscopical studies of material obtained by puncture and suction before ulceration and by swab smears after ulceration. Even though death occurred very early (average of nineteen days) in these animals, *Mycobacterium tuberculosis* was widely diffused; so were the streptococci and staphylococci. Neither spirochetes nor *Micrococcus catarrhalis* were generalized.

In animals No. 4 and 8 in table 5, osteomyelitis with ulcerations developed from which *Mycobacterium tuberculosis, Staphylococcus aureus* and coliform organisms were isolated. There were several abscesses of the abdominal wall in this series with sinuses leading down to the site of peritoneal adhesions. Sub-

TABLE 4

Guinea pigs inoculated with Mycobacterium tuberculosis and Staphylococcus aureus

GUINEA PIG NUMBER	ULCERATION AT SITE OF INOCULATION	DEATH	PRESENCE OF "SECONDARY" ORGANISMS IN S, L, LN AND O AT AUTOPSY	PRESENCE OF MYCBACTERIUM TUBERCULOSIS IN S, L, LN AND O AT AUTOPSY
		days		
1	+	41	S..... 0 L..... 0 LN..... 0 O..... 0	S..... + L..... + LN..... + O..... +
2	+	40	S..... + L..... 0 LN..... 0 O..... +	S..... + L..... + LN..... + O..... +
3*	+	40	S..... + L..... 0 LN..... + O..... +	S..... + L..... + LN..... + O..... +
4	+	42	S..... + L..... + LN..... + O..... +	S..... + L..... + LN..... + O..... +
5	−	51	S..... + L..... + LN..... + O..... +	S..... + L..... + LN..... + O..... +
6*	+	31	S..... + L..... + LN..... + O..... +	S..... + L..... 0 LN..... + O..... 0
7	−	37	S..... + L..... + LN..... + O..... +	S..... + L..... + LN..... + O..... 0
8	+	39	S..... 0 L..... + LN..... + O..... +	S..... + L..... + LN..... + O..... 0
9*	+	36	S..... + L..... + LN..... + O..... +	S..... + L..... + LN..... + O..... 0
10	−	45	S..... + L..... + LN..... + O..... +	S..... + L..... + LN..... + O..... 0

TABLE 4—(*Continued*)

GUINEA PIG NUMBER	ULCERATION AT SITE OF INOCULATION	DEATH	PRESENCE OF "SECONDARY" ORGANISMS IN S, L, LN AND O AT AUTOPSY	PRESENCE OF MYCOBACTERIUM TUBERCULOSIS IN S, L, LN AND O AT AUTOPSY
		days		
11	−	42	S..... +	S..... +
			L..... +	L..... +
			LN..... +	LN..... +
			O..... +	O..... 0
12*	−	26	S..... +	S..... 0
			L..... +	L..... 0
			LN..... +	LN..... +
			O..... +	O..... 0

acute serofibrinous peritonitis was present in most of the animals showing abscesses of the abdominal wall and intraperitoneal adhesions. *Mycobacterium tuberculosis* was obtained from both the peritoneal cavities and the mesenteric lymph nodes.

The streptococci, which were frequently found in the joint cavities in series III where fully virulent, pure cultures of *Streptococcus viridans* were used, were conspiciously absent in this series. The strain of streptococcus used in series V was either not the type that show elective affinity for the endothelially lined cavities, or the rapidly fatal course of the disease did not permit allergic elective localization. Of course, there is always a probability of effective bacterial antagonism whenever microörganisms are sealed in a small cavity by inoculation or the organisms may have been one of the nonpathogenic streptococci of the mouth.

DISCUSSION

Many clinicians in charge of patients with pulmonary tuberculosis do not give much thought to the control of "secondary" organisms of the mouth and upper respiratory tracts. Experimental evidence here seems to reemphasize the importance of pathogenic *Streptococcus viridans* and *Staphylococcus aureus* in the clinical pathology of tuberculosis. *Streptococcus viridans* acts as a body sensitizer which interferes with effective fibroblastic action in walling off *Mycobacterium tuberculosis*. The spread of *Mycobacterium tuberculosis* is hastened and the tissue damage is greater. The necrotoxic action of *Staphylococcus aureus* and the systemic action of other fractions of the toxins from these "secondary" organisms interfere with the effective reticulo-endothelial responses necessary to the arrest of such diseases as tuberculosis. In many of the cases of pulmonary tuberculosis the patient has a chronic sinusitis or other focus in which staphylococcus or streptococcus is the chief organism. The treatment of such foci by surgery, chemotherapy or biologicals should be an essential part of the management of pulmonary tuberculosis. We feel that such a modification in the management of cases would contribute materially to the arrest of the process and hasten the convalescence.

TABLE 5

Guinea pigs inoculated with 0.5 cc. of undigested sputum from D.H. # A-7230 containing the following organisms:*
Mycobacterium tuberculosis—Gaffky 5
Staphylococcus aureus
Streptococcus nonhaemolyticus
Neisseria catarrhalis
Saprophytic spirochetes
Nonpathogenic yeast

GUINEA PIG NUMBER	ULCERATION AT SITE OF INOCULATION	DEATH	PRESENCE OF "SECONDARY" ORGANISMS IN S, L, LN AND O AT AUTOPSY	PRESENCE OF MYCOBACTERIUM TUBERCULOSIS IN S, L, LN AND O AT AUTOPSY
		days		
1	+	15	S..... + L..... + LN..... + O..... +	S..... + L..... + LN..... + O..... 0
2	+	19	S..... + L..... + LN..... + O..... +	S..... + L..... + LN..... + O..... +
3	+	27	S..... + L..... + LN..... + O..... +	S..... + L..... + LN..... + O..... +
4	+	13	S..... + L..... + LN..... + O..... +	S..... + L..... + LN..... + O..... +
5	+	14	S..... + L..... + LN..... + O..... +	S..... + L..... + LN..... + O..... +
6	+	31	S..... + L..... + LN..... + O..... +	S..... + L..... + LN..... + O..... +
7	+	9	S..... + L..... + LN..... + O..... +	S..... + L..... 0 LN..... + O..... 0
8	+	18	S..... + L..... + LN..... + O..... +	S..... + L..... + LN..... + O..... 0

* The oral hygiene was poor in D.H. # A-7230.

TABLE 5—(*Continued*)

GUINEA PIG NUMBER	ULCERATION AT SITE OF INOCULATION	DEATH	PRESENCE OF "SECONDARY" ORGANISMS IN S, L, LN AND O AT AUTOPSY	PRESENCE OF MYCOBACTERIUM TUBERCULOSIS IN S, L, LN AND O AT AUTOPSY
		days		
9	+	20	S..... +	S..... +
			L..... +	L..... +
			LN..... +	LN..... +
			O..... +	O..... 0
10	+	28	S..... +	S..... +
			L..... +	L..... +
			LN..... +	LN..... +
			O..... +	O..... +
11	+	20	S..... +	S..... +
			L..... +	L..... +
			LN..... +	LN..... +
			O..... +	O..... +
12	+	11	S..... +	S..... +
			L..... +	L..... 0
			LN..... +	LN..... +
			O..... +	O..... 0

SUMMARY AND CONCLUSIONS

From a protocol in which 60 guinea pigs were used in the major experiment and 15 were used as checks and confirmation, it is shown that the presence of *Monilia candida* in a tuberculous guinea pig does not materially alter the course of the disease. The course of the disease was significantly changed when pure cultures of *Streptococcus viridans* or *Staphylococcus aureus* were injected along with *Mycobacterium tuberculosis*. The action appeared to be synergistic.

In cases where the "secondary" microörganisms, frequently seen in those with poor oral hygiene, were injected along with *Mycobacterium tuberculosis*, the clinical course and pathological findings in guinea pigs were significantly different from those injected with *Mycobacterium tuberculosis* alone. The course, in the former, was a rapidly fatal one in contradistinction to the slowly progressive course in those infected with *Mycobacterium tuberculosis* without these "secondary" microörganisms. The presence of *Streptococcus viridans* or *Staphylococcus aureus* associated with tuberculosis interfered with the defense of the body against *Mycobacterium tuberculosis*.

SUMARIO Y CONCLUSIONES

Por un protocolo en que se utilizaron 60 cobayos en el experimento principal, y 15 para comprobación y confirmación, demostróse que la presencia de *Monilia candida* en un cobayo tuberculoso no afecta mayor cosa la evolución de la dolencia. En cambio ésta se alteró significativamente cuando se inyectaron junto con el *Mycobacterium tuberculosis*, cultivos puros de *Streptococcus viridans* o *Staphylococcus aureus*, pareciendo el efecto de orden sinérgico.

En los casos en que junto con el *Mycobacterium tuberculosis*, se inyectaron los microbios "secundarios" que se observan frecuentemente en los casos de deficiente higiene bucal, la evolución clínica y hallazgos positivos en los cobayos variaron de los observados en aquéllos a los que sólo se les inyectó el *Mycobacterium tuberculosis*. En los primeros, la evolución fué rápidamente letal, en contraposición a la evolución lentamente progresiva en los infectados con el *Mycobacterium tuberculosis* sin aquellos gérmenes "secundarios." La presencia del *Streptococcus viridans* o *Staphylococcus aureus* en asociación con la tuberculosis, obstaculizó las defensas orgánicas contra el *Mycobacterium tuberculosis*.

I wish to express appreciation to Miss Johnay B. Walker, laboratory technician, Freedmen's Hospital Tuberculosis Annex, for helping me with the collection and analysis of the sputum from patients in the hospital.

BLOOD PHOSPHATASES AND ACID-SOLUBLE PHOSPHORUS IN EXPERIMENTAL TUBERCULOSIS[1]

M. I. SMITH AND B. B. WESTFALL

The problem of mineral metabolism in tuberculosis has received considerable attention; not so the question of phosphorus metabolism. In many ways the metabolism of calcium and phosphorus are so closely interrelated that no clear understanding of the one may be had without due regard for the other. Binger (1) showed that the intravenous injection of phosphate not only increases the serum phosphorus but correspondingly decreases the serum calcium. This is accompanied by increased phosphorus excretion in the urine with reduced calcium output (2). The ultimate fate of calcium under such conditions is not known, though the possibility of an increased rate of fixation in the tissues as colloidal calcium phosphate has some experimental evidence (3). The phagocytosis of such colloidal calcium by the macrophages of the liver and spleen (4) may conceivably constitute one phase in the mechanism of calcification of the tubercle, which is generally regarded as an essential factor in the natural defenses of the body in checking the spread of the disease process.

On the assumption that the inorganic phosphorus of the blood may be regulated to some extent by the phosphatases of the blood which in turn may influence the circulating and tissue calcium, we undertook a study of the plasma and red blood cell phosphatases in relation to the acid-soluble phosphorus of the blood in experimentally infected guinea pigs as compared with normal animals. It seems possible, as pointed out by Guest and Rapoport (5), that the organic phosphoric esters of the red blood cells might serve as a reservoir of readily available labile phosphorus, which through dephosphorylation could furnish inorganic phosphorus for tissue utilization. These authors discuss the various factors concerned with increase or decrease of organic phosphorus in erythrocytes, though they do not consider the possible rôle of phosphatase in this connection.

METHODS AND MATERIAL

Plasma phosphatase determinations were made upon oxalated plasma by the method of Bodansky (6) with β-glycero-phosphate as substrate in barbital buffer at pH 9.0 and magnesium chloride as activator. A sixty-minute period of incubation at 37°C. was used in all cases. Erythrocyte "acid" phosphatase was determined upon washed cells, haemolyzed 1:3 with water, in an acetate buffer at pH 5.0 with the same substrate as for plasma phosphatase. The acid soluble phosphorus fractions were determined in the trichloracetic acid filtrates obtained by precipitation of a weighed amount of whole blood with cold 5 per cent CCl_3COOH in an approximate dilution of 1:11. The inorganic phosphorus was determined directly in the filtrate, and the easily hydrolyzable fraction after hydrolysis of 2 cc. of filtrate with 0.25 cc. 10 *N* sulfuric acid in

[1] From the Division of Chemotherapy, National Institute of Health, U. S. Public Health Service, Bethesda, Maryland.

boiling water for seven minutes (7). The total acid soluble phosphorus was determined in 0.5 cc. of the filtrate after oxidation with sulfuric acid and hydrogen peroxide. The difference between the total and the sum of inorganic plus easily hydrolyzable is considered as ester phosphorus. Since inorganic phosphorus occurs for the most part in plasma and organic for the most part in the red blood cells (5) all the inorganic is expressed in mg. per 100 cc. of the plasma and all the organic on the red cell basis as determined by the haematocrit.

Guinea pigs of both sexes weighing usually 400 to 600 g. were used. The animals were kept on a diet of Purina rabbit chow supplemented with cabbage twice weekly to supply vitamin C. Blood samples were obtained by cardiac puncture. The tuberculous animals used in these experiments were guinea pigs that had been infected two to three months previously by intraperitoneal inoculation of 0.5 mg. moderately virulent human strain A27 (Phipps Institute). Upon completion of the experiment the animals were killed and autopsied. The necropsy findings uniformly showed moderate to advanced tuberculosis of the viscera, including lymph nodes, omentum, spleen, liver and lungs.

RESULTS

Table 1 gives the data on haematocrit, plasma and erythrocyte phosphatases, the plasma inorganic phosphorus and the red cell hydrolyzable and ester phosphorus in a series of 10 normal guinea pigs. In table 2 similar data are given for a series of 11 tuberculous guinea pigs. A comparison of the data of the two tables indicates the following points of difference.

1. The haematocrit in the tuberculous animals was usually below normal. This may be ascribed to the secondary anaemia.

2. The plasma phosphatase in the infected animals was much more variable. The values were frequently below normal which may in part be accounted for by impaired nutrition, since fasting is known to decrease the "alkaline" phosphatase (8). In some of the experiments, however, the values were well above normal. Interestingly, the highest values were associated with the lower haematocrit values recorded.

3. Red cell ester phosphorus was more variable and with few exceptions consistently higher in the tubercle infected animals as compared with the controls. The high ester values were usually, though not necessarily, associated with low haematocrit values. No reticulocyte counts were made, but it is probable that the high ester values may have been the result of reticulocytosis associated with the anaemia. The adenosine triphosphate content of red blood cells is said to increase with reticulocytosis such as might follow haemorrhage or phenylhydrazine administration (5).

The red cell "acid" phosphatase and the easily hydrolyzable organic phosphorus fraction were quite variable in both groups of animals with little difference as between the groups. The inorganic phosphorus fraction was on the whole more uniform in the controls.

The possibility of partial inanition in the tuberculous animals being responsible for some of the results led us to examine these factors in a small series of 4 normal guinea pigs fasting for a period of from two to four days. The

plasma phosphatase was lower in this group, as might be expected, an average of 4.0, while the haematocrit was higher, an average of 47, probably due to anhydraemia. No differences from the normal were noted in either the red

TABLE 1

Phosphatases and phosphorus distribution in the blood of normal guinea pigs

NUMBER	HAEMATOCRIT	PLASMA PHOSPHATASE	RED CELL PHOSPHATASE	PLASMA INORGANIC PHOSPHORUS	RED CELL PHOSPHORUS	
					Hydrolyzable	Ester
1	46	3.0	15.0	4.3	6.5	30.5
2	46	5.5	12.0	5.2	8.7	59.0
3	39	9.0	12.5	7.2	10.2	44.0
4	40	4.5	18.0	2.2	11.3	70.0
5	50	3.5	10.0	5.0	6.0	30.0
6	34	4.5	11.0	5.5	16.2	82.5
7	38	6.0	10.0	6.8	1.3	45.0
8	40	8.0	18.5	8.2	5.8	75.0
9	43	7.0	21.5	7.7	5.8	51.0
10	39	8.0	8.0	5.1	3.8	56.0
Average	41.5	5.9	18.7	5.7	7.6	54.2
Standard Deviation	4.2	2.54	4.18	1.7	4.0	16.8

TABLE 2

Phosphatases and phosphorus distribution in the blood of tuberculous guinea pigs

NUMBER	HAEMATOCRIT	PLASMA PHOSPHATASE	RED CELL PHOSPHATASE	PLASMA INORGANIC PHOSPHORUS	RED CELL PHOSPHORUS	
					Hydrolyzable	Ester
1	26	2.5	17.0	3.5	12.5	86.0
2	42	3.5	15.5	6.9	12.0	43.0
3	30	5.0	26.0	18.5	1.7	150.0
4	38	6.0	19.5	4.2	7.9	174.0
5	26	4.0	13.0	3.8	7.7	69.0
6	32	2.5	22.0	5.9	6.3	38.0
7	25	6.0	15.0	3.9	8.0	84.0
8	25	8.0	9.5	6.0	12.0	88.0
9	31	8.5	9.0	3.9	8.1	56.0
10	17	12.0	15.0	3.1	8.8	142.0
11	22	27.5	18.5	5.1	6.8	77.0
Average	29	7.8	16.5	5.9	8.3	91.6
Standard Deviation	6.9	6.8	4.8	4.1	2.9	42.4

cell phosphatase (average 16.3), or the ester phosphorus (average 63.0). The easily hydrolyzable phosphorus, average 4.5, was somewhat lower compared with the controls probably accounting for the slightly elevated inorganic phosphorus fraction which was on an average 7.0 mg. per cent.

SUMMARY

A study of the blood phosphatases in relation to the acid-soluble phosphorus distribution in the blood of experimentally infected tuberculous guinea pigs showed a deviation from the normal pattern characterized chiefly by a variable and generally elevated plasma phosphatase and a marked increase in the ester phosphorus fraction of the red blood cells. The latter seems to be accounted for by the secondary anaemia, as evidenced by relatively low haematocrit values. The plasma inorganic phosphorus, though more variable, was on an average no different from that of the controls.

SUMARIO

Un estudio de la fosfatasa sanguínea en relación con la distribución de fósforo ácidosoluble en la sangre de los cobayos tuberculosos infectados experimentalmente, reveló una desviación del patrón normal, caracterizado principalmente por una variación y elevación general de la fosfatasa plasmática y un aumento acentuado de la fracción esterofosfórica de los hematíes. Puede explicarso lo último por la anemia secundaria, según revelan las cifras relativamente bajas del hematocrito. El fósforo inorgánico del plasma, aunque más variable, en conjunto no se diferencia del de los testigos.

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A SENSITIVE LONGEVITY-IMMUNITY TEST WITH GUINEA PIGS

WILLIAM N. BERG[1]

THE PROBLEM

Let it be assumed that a large group of young children with fatal infection have received a specific treatment. Although many were benefited, large numbers did not survive as long as some of those without specific therapy. All were infected at about the same age, three years.

The reason for assuming the age of the children to be about three years when infected is that guinea pigs usually are three to four months old when used in a test. Guinea pigs live about as many months as people live years, so that the three months old guinea pig approximates the three year old child. One of Eaton's (1) guinea pigs, out of about 30,000, attained the age of ninety-two months.

It is desired to test the treatment with guinea pigs, so as to answer these questions: (*1*) Did the treatment prolong life? (*2*) By how much? (*3*) Will the conclusions be confirmed by the next investigator? The main requirement of the proposed method is virulence measurement of the dose by the use of a control group of at least 40 males. This provides a statistical basis for comparison with one or several treatment groups of 10 each.

STEPS IN THE TEST

Step 1: The control group. Not less than 40 males should be used. Life expectations of females are lower than those of males (Berg (2)), hence indeterminate mixing may impair the test. The standard deviation from mean survival-time is to be calculated for use in step 4. The limited value of this statistic for the present purpose, when calculated from less than 40 survival-times, is discussed by Treloar (3). To learn how to calculate a standard deviation requires about thirty minutes; the method is shown in Snedecor's (4) and other texts.

An example of a control group is shown in table 1. The results were obtained by Birkhaug (5). His table is reproduced in full because it is used as an example in the calculations to follow. The first reason for selecting this group of 48, out of many others that were studied, is that only 4 died of intercurrent infection. It must be assumed that correct laboratory technique is not disturbed by intercurrent infections, fighter guinea pigs or other influences. The group is here considered as a single distribution of 44 control survival-times, since no (?) immunity was found. The reason for the question mark is discussed at the end of the paper.

Step 2: What is the mean survival-time? Birkhaug computed four means: 107, 118, 121.7 and 126 days. If 1,000 groups of 10 guinea pigs had been infected, what would the smallest and largest means be? This can only be guessed at so long as one is limited to data from unrelated small control groups

[1] 789 West End Avenue, New York City.

of about 10. When 40 or more control guinea pig survival-times in one test are available, simple statistical calculations will answer the above question. This is shown in diagram 1.

TABLE 1

Birkhaug's data

Survival-time, in days, of tuberculous guinea pigs treated with cod-halibut-liver oils
Infection dose: 0.000, 01 mg. bovine tubercle bacilli

"SENJA"	"SQUIBB"	"LEVER"	CONTROLS
days	*days*	*days*	*days*
76	87	78	63
83	94	93	68
86	112	115	72
104	112	118	84
106	114	124	90
118	131	124	104
128	135	125	107
133	141	131	125
133	160	146	138
136	176	163	138
149	Int.*	Int.	146
158	Int.	Int.	148
Experiment mean.....118	126	121.7	107
Control mean.....107	107	107	
Difference..... 11	19	14.7	
Standard deviation.... 25.47	26.58	22.79	
t..... 0.924	1.475	1.205	
n..... 22	20	20	
P..... 0.32	0.18	0.24	

* Early death from intercurrent infection.

DIAGRAM 1

Showing the distribution of mean survival-times of groups of 10 control guinea pigs similar to table 1

Base line of curve of means							
Mean survival-time (days)...	91	100	109	118	126	135	144
Probability of obtaining above mean, or a greater mean...	.999	.977	.841	.500	.159	.023	.001
Standard deviations, curve of means.....	−3	−2	−1	0	1	2	3

If table 1 had listed 1,000 groups, each with 10 survival-times, instead of only 4 groups, the mean survival-times would vary from 91 to 144 days. These are plotted on the base line. In the 1,000 means, one will be 144 days or greater, 23 means will be 135 days or greater, etc.

Diagram 1 indicates the futility of attempting to measure the virulence of a culture by infecting one or two small groups of guinea pigs. The base line cannot

be generalized: the mean survival-times must be calculated anew from each experiment. The statistical steps used to bring table 1 into diagram 1 now follow.

Step 3: Calculate the standard deviation from mean survival-time, 117.55 days, for the distribution of 44 survival-times. This was 27.82 days.

Step 4: Calculate the standard error of the mean survival-time. The formula is in Snedecor (4), page 50. The standard error was 8.80 days, that is, 27.82 was divided by the square root of 10; 10 being the number of guinea pigs in one treatment group. The rounded value, 9 days, is the interval on the base line of diagram 1. Plotting this line starts with placing a point near its centre to represent the mean of the 44 survival-times.

Step 5: Calculate the highest control mean survival-time for comparison with a treatment mean survival-time. This is the critical figure. To the control mean survival-time, add three times the standard error. For table 1 this was $117.55 + 3 \times 8.80$ or 143.95 days. The rounded number, 144 days, may be taken to mean that, had the identical tubercle bacillus suspension been injected in equal doses of 0.000,01 mg. into 1,000 groups of 10 guinea pigs, the mean survival-time would have been 144 days or more, in one group.

INTERPRETATION OF RESULTS

Let it be assumed that a virulence measurement has been made, using 40 or more male guinea pigs as a control group which gave the figures in diagram 1. Assume further that a treatment group of 10 males gave a mean survival-time of 155 days. The three questions asked in the statement of the problem, in the beginning of this paper, can now be answered.

(*1*) Did the treatment prolong life? The investigator can compare the treatment mean, here assumed to be 155 days, with any mean from 91 to 144 days on the base line of diagram 1. If workers agreed to use the maximum control mean survival-time, it could serve as a basis for comparisons. When samples of 10 and 10 guinea pigs are used, the investigator compares the treatment mean with one of the control means on the base line without having any idea where the other control means are. The t-test will tell what is the probability that both means lie on the same base line, that is, they do or do not belong to the same population of means. But there is no measurement.

The *second* question, by how much was life prolonged, cannot, of course, be answered for an individual. For the treated group, the difference between means in this assumed example, 155 less 144 days, could be translated into 11/30 of a year, using one month in the guinea pig as equivalent to one year in a person. This would be conservative because the prolongation is measured from the maximum control mean survival-time.

The *third* question, will the conclusions be confirmed by the next investigator, can be answered in the affirmative, provided that the principal requirement of the method be met. This is virulence measurement, rather than testing. The base line of diagram 1 will vary, even if the same suspension and dose were used in the same hour in different laboratories. But in all cases, the conclusion that

immunity was produced will be based on a treatment mean having exceeded the maximum control mean obtained at the same time. Comparisons will be facilitated if, in addition to publishing every individual survival-time, there is also a statement of the number of living and dead tubercle bacilli in the dose.

Taking Birkhaug's table 1 as it stands, a comparison can be made between the 12 controls as one group and the 32 codliver oil treated guinea pigs as a second group. The t-test gives $\frac{1}{2}$ P equal to 0.06, and one cannot be too sure that there was no immunity. The successive steps in calculating the t-test have been described previously (6). These can be learned in a short time.

Theoretical aspects of the foregoing method can be found in the publications of Maynard (7) and of Greenwood and Yule (8).

CONCLUSIONS

In the proposed longevity-immunity test with guinea pigs, the steps are:

1. Measure the virulence of the dose, using not less than 40 males. Publish all individual survival-times, in days.
2. Measure the virulence of the dose, as modified by treatment, in one or more groups of not less than 10 males.
3. For the control group calculate the standard deviation from mean survival-time.
4. Calculate the standard error of the control mean survival-time.
5. Calculate the highest control mean survival-time.
6. Compare the highest control mean survival-time with the mean survival-time of a treatment group.

CONCLUSIONES

En la prueba propuesta para determinar la longevidad e inmunidad de los cobayos, los tiempos sucesivos son:

1. Mídase la virulencia de la dosis, empleando no menos de 40 machos, y exprésense en días todos los tiempos de sobrevivencia de los distintos sujetos.
2. Mídase la virulencia de la dosis, según la modifica el tratamiento, en uno o más grupos de no menos de 10 machos.
3. Para el grupo testigo, calcúlese la desviación tipo del tiempo de sobrevivencia media.

Calcúlese el error tipo del tiempo medio de sobrevivencia en los testigos.

5. Calcúlese el máximo tiempo medio de sobrevivencia en los testigos.
6. Compárese el tiempo medio máximo de sobrevivencia en los testigos con el tiempo de sobrevivencia media en un grupo tratado.

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AMERICAN TRUDEAU SOCIETY

Contact Examinations

The Contact Infection Committee of the American Academy of Pediatrics recommends to pediatricians the following program, which has been approved by the Executive Committee of the American Academy of Pediatrics and the Executive Committee of the American Trudeau Society:

1. Every child should be tuberculin tested at frequent intervals, and best annually, as long as he remains negative.
2. Adult family members and domestic workers should have chest X-ray films unless their tuberculin tests have been found negative. Tuberculin testing of these adults may be done by the pediatrician at the same time that the children are being tested, or preferably, whenever possible, by another physician.
3. Whenever a child is found to have a positive tuberculin reaction it is *urgent* that all adults closely associated with this child should have a thorough examination in an effort to find the source of infection.
4. Examination for tuberculosis of adults who have shown positive reactions should not be made by the pediatrician but by qualified specialists in this disease.
5. Open cases of tuberculosis should be segregated and removed from children until there is no longer danger of dissemination of tubercle bacilli.
6. When a case of open tuberculosis is found in a family all children in contact with the patient who have not previously shown a positive tuberculin reaction should be tested. Those who are negative at this time should be retested after a period of three months from the time of the last exposure.

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